

# Evidence summaries: unlicensed and off-label medicines – Interim process statement

Process and methods

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[www.nice.org.uk/process/pmg2](http://www.nice.org.uk/process/pmg2)



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# 1 Introduction

This is not the current process. From May 2013, evidence summaries: unlicensed and off-label medicines were developed using the [integrated process statement](#).

## 1.1 Introduction to interim process statement

This interim process statement has been produced to guide the development of 'Evidence summaries: unlicensed and off-label medicines' (ESUOMs). It provides an overview of the key process principles and describes all stages of development for ESUOMs. These procedures are designed to ensure that a robust, quality-assured, commentary is developed for the NHS in an open, transparent and timely way, with appropriate input from key groups.

ESUOMs support the use of unlicensed and off-label medicines for individual patients, where there are good clinical reasons for the use of an off-label or unlicensed medicine, usually when there is no licensed medicine for the condition requiring treatment, or it is not appropriate for that individual. **They should not be considered to promote the use of unlicensed medicines solely for economic reasons.**

This interim process statement of ESUOMs will be superseded when the final process guide is issued later in 2012, following engagement and discussions with key groups.

## 1.2 Background to 'Evidence summaries: unlicensed and off-label medicines'

The National Institute for Health and Clinical Excellence (NICE) is part of the NHS. NICE's evidence-based guidance and other products help resolve uncertainty about which medicines, treatments, procedures, technologies and devices represent the best quality care and offer the best value-for-money for the NHS. Further information about NICE and its work is available on the NICE website ([www.nice.org.uk](http://www.nice.org.uk)).

The NICE Medicines and Prescribing Centre provides advice and support for delivering safety, efficiency and effectiveness in the use of medicines. The Medicines and Prescribing Centre is responsible for developing the ESUOMs.

ESUOMs will provide a summary of the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. This will provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies. The strengths and weaknesses of the relevant evidence will be critically reviewed within each ESUOM. Importantly, **an ESUOM does not constitute NICE guidance** and this will be clearly stated on each publication. This information from NICE will help to avoid potential duplication of effort where, currently, different NHS organisations produce similar products for their own local use.

The topics for ESUOMs are selected in collaboration with the existing NICE topic selection programme. Two types of topics are considered:

- an unlicensed medicine: that is, a medicine that does not have a UK marketing authorisation and is not expected to do so in the next 2 years.
- an off-label medicine: that is, a medicine with an existing UK marketing authorisation that is used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population.

## 2 Evidence summaries: unlicensed and off-label medicines

### 2.1 Aims

The aim of an ESUOM is to provide information about an unlicensed or off-label medicine that is being considered for use in circumstances where there are no clinically appropriate licensed alternatives. The ESUOM helps inform decision-making by clinicians and patients and supports the construction and updating of local formularies.

### 2.2 Key audiences

ESUOMs are produced specifically for:

- clinicians, to inform their decision-making
- patients and the public, to inform their decision-making
- local decision-making groups involved in commissioning, policy development, or individual funding requests (IFRs), for example, within a Clinical Commissioning Group (CCG) or NHS Trust.

### 2.3 Key activities

The key activities involved in the production of each ESUOM are:

- identifying, prioritising and selecting the topic
- summarising the published evidence
- critically reviewing the strengths and weaknesses of the evidence
- placing the evidence in the context of the wider evidence base, for the management of the condition for which the unlicensed or off-label use is being considered, particularly NICE guidance, where available

- highlighting any potential implications for local decision-making or clinical practice
- producing a summary for patients for each ESUOM
- identifying any new evidence relevant to published ESUOMs through scanning the literature, reviewing and, if necessary, updating or withdrawing an ESUOM (see [section 6](#)).

NICE holds a contract with an external supplier to produce ESUOMs to an agreed process and standard (see [section 3.2](#)).



## 3 Who is involved in producing 'Evidence summaries: unlicensed and off-label medicines'?

### 3.1 The Medicines and Prescribing Centre

The Medicines and Prescribing Centre is part of NICE's Centre for Clinical Practice (CCP). The Medicines and Prescribing Centre consists of a programme director, associate directors and clinical, technical, project and administrative staff. For ESUOMs, senior members of the Medicines Evidence team within the Medicines Prescribing Centre are responsible for:

- developing and reviewing processes and methods for producing ESUOMs
- identifying potential topics for ESUOMs in collaboration with the NICE Topic Selection team
- liaising with the contracted external supplier to ensure ESUOMs are developed and prepared for publication in line with the agreed process and standards
- liaising with the contracted external supplier to identify external specialist commentators to help ensure the content is relevant and useful
- providing quality assurance of the content of ESUOMs
- ensuring timelines and quality assurance standards are followed
- liaising with the external supplier to review and update content of published ESUOMs, where required.

### 3.2 External supplier

Following a tendering process conducted in early 2012, NICE holds a contract with an external supplier to write ESUOMs to an agreed process and standard. The Medicines and Prescribing Centre manages the contract with the external supplier. In summary, the role of the external supplier is to search for and sift the evidence, critically appraise the

evidence, develop a draft and liaise with expert reviewers. The role will be fully defined in the final version of the process guide.

### **3.3 The NICE Patient and Public Involvement Programme**

The Patient and Public Involvement Programme (PIIP) provides NICE with advice on involving patients, carers and members of the public. The role of the PIIP team in the ESUOM programme, is to provide editorial input into the summary for patients as well as helping to identify expert patients, or commentators from patient organisations or groups<sup>[1]</sup>, to input into the topic selection and content of the summary for patients.

### **3.4 Other NICE teams**

In addition to the PIIP, to develop ESUOMs, the Medicines and Prescribing Centre works closely with members of other NICE teams to avoid overlap with other programmes and potential duplication of effort. These include; Topic Selection, Technology Appraisals, Clinical Guidelines, Communications (including Publishing), Evidence Information Services and Guidance Information Services. Their roles will be defined in the final version of the process guide.

### **3.5 Unlicensed and Off-label Medicines (UOM) Prioritisation Panel**

The UOM Prioritisation Panel has a standing membership, who advise NICE on topics that should be prioritised for development as an ESUOM. Members of the panel are being sought from existing commissioning, medicines and pharmacy networks, and include; lay members, representatives from the Association of the British Pharmaceutical Industry (ABPI), the Medicines and Healthcare products Regulatory Agency (MHRA) and the Royal College of Paediatrics and Child Health (RCPCH). Once in place, the membership of the panel will be available on the NICE website.

### **3.6 External specialist commentators**

The specialist commentator(s) are identified to review draft ESUOMs ahead of publication. They are practitioners who have significant expertise in the therapeutic area for which the

unlicensed or off-label medicine is to be used. Their role is to clarify any issues about the reviewed evidence and the practical implications of the information contained in the ESUOM. Suggestions for appropriate external specialist commentators come from existing NICE networks, the external supplier, national professional organisations and the New Medicines Community of Practice (see [section 3.9](#)).

## 3.7 Manufacturers

When a topic is selected for the ESUOMs programme, NICE informs the manufacturer<sup>[2]</sup> of the medicine of its intention to produce an ESUOM and the expected timeframe for production. NICE invites them to provide relevant information to support the production of the ESUOM.

The manufacturer is also invited to comment on a draft of the ESUOM, and provides comments within an agreed time frame. The manufacturer has the opportunity to comment on matters of factual accuracy, and respond to any specific questions from NICE about the information they submitted to inform the development of the ESUOM.

## 3.8 The Medicines and Healthcare products Regulatory Agency (MHRA)

The NICE Medicines and Prescribing Centre contacts the MHRA (or the European Medicines Agency [EMA], as appropriate) to ask for any evidence on the topic held on file that is not confidential. They will be invited to comment on a draft of the ESUOM, and provide comments within a short time frame. Their role is to comment on regulatory and safety issues within the topic covered by the ESUOM.

## 3.9 The NICE Medicines and Prescribing 'New Medicines Community of Practice'

The New Medicines Community of Practice was established by the Medicines and Prescribing Centre, to support those NHS staff with a role in local policy making on medicines and prescribing, including the use of unlicensed and off-label medicines. This is a group consisting of about 300 healthcare professionals, who are actively involved in local decision-making bodies such as, Area Prescribing Committees.

The New Medicines Community of Practice assist with the identification of topics (see [section 4.1](#)), and help to identify external specialist commentators, who may come from the Community of Practice itself.

## 3.10 Conflicts of interest

NICE staff, the external supplier, members of UOM Prioritisation Panel, the New Medicines Community of Practice and specialist commentators will be required to comply with the NICE code of conduct on conflicts of interest. For more information about how NICE deals with conflicts of interest, please see '[A code of practice for declaring and dealing with conflicts of interest](#)'.

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<sup>[1]</sup> NICE uses the terms 'patient organisation' and 'patient group' to include patients, carers, and community and other lay organisations, including those representing people from groups protected by equalities legislation

<sup>[2]</sup> For some unlicensed or off-label medicines, more than one manufacturer may be involved in the development of the drug. On these occasions, all relevant manufacturers based in the UK will be contacted for information.

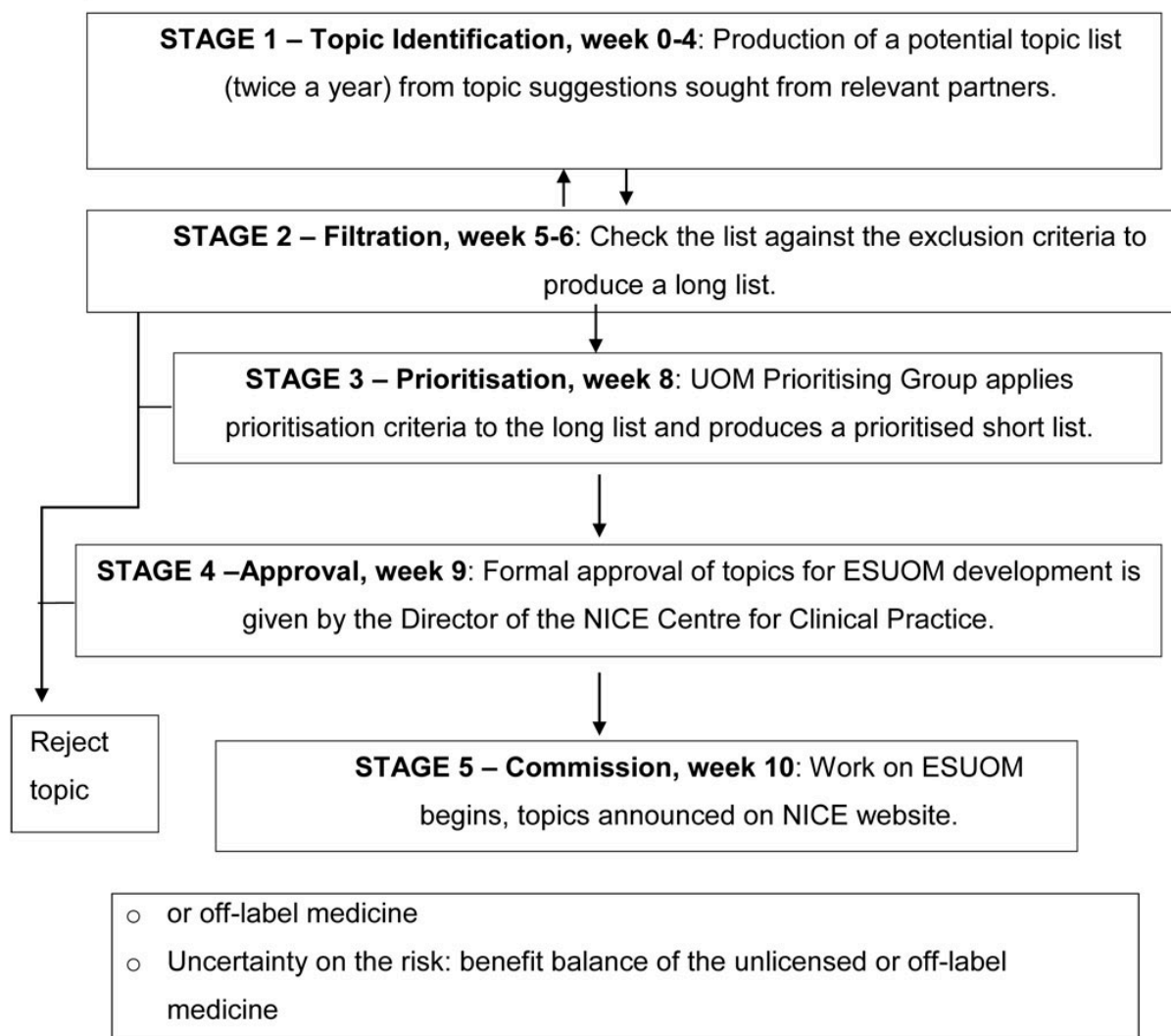
## **4 Topic identification, prioritisation and selection**

### **4.1 Topic identification and prioritisation**

The NICE topic selection programme is responsible for managing the process of topic identification, prioritisation and selection for ESUOMs. Topics will be selected where a demand for information has been identified.

There is no established horizon scanning service to identify potential topics for this work stream. A new approach to gathering this information is therefore required.

**Figure 1: Flow-chart showing main steps in process for topic identification, prioritisation and selection for ESUOM**



## Stage 1: Identifying potential topics

Partner organisations<sup>[3]</sup> are approached twice a year to suggest potential topics. They are asked to consider the exclusion criteria in Box 1 when suggesting topics. These criteria are designed to filter out topics unsuitable for development into an ESUOM and ensure each topic selected will add value.

### **Box 1 Long list: exclusion criteria**

- There is a clinically appropriate licensed alternative and use of the unlicensed or off-label medicine is being proposed on solely economic grounds
- The topic is a variation in delivery route or a modification to a formulation already licensed
- The topic covers population screening, immunisation or HIV treatment (as these are normally covered by other bodies)
- High-quality reviews/guidance are already available from a NICE-accredited source
- A marketing authorisation is being sought and expected to be granted within 2 years

The suggestions from the partner organisations and any other potential topics identified through NICE networks, are compiled to form a list of potential topics.

### **Stage 2: Filtration: applying the exclusion criteria**

The NICE Topic Selection team and the Medicines and Prescribing Centre check the potential list of topics against the exclusion criteria (see box 1). Topics that meet the exclusion criteria are removed from the list and a long list for prioritisation is created.

### **Stage 3: Prioritisation: developing the short list**

The UOM Prioritisation Panel (see [section 3.5](#)) meets twice a year to consider the priority for each topic on the long list. They advise NICE on the priority of each topic using the prioritisation criteria in Box 2.

### **Box 2 Short List: prioritisation criteria**

- High volume of requests from the NHS for information on the topic
- Large variations in clinical practice, significant divergence of clinical opinion and/or reports of difficulty of access to the unlicensed or off-label medicine
- Uncertainty on the risk:benefit balance of the unlicensed or off-label medicine

The advice from the UOM Prioritisation Panel is considered by NICE and used to produce the short list of topics that NICE intend to develop as ESUOMs.

#### **Stage 4: Approval:**

The short list of potential ESUOM topics is sent to the Director of the NICE Centre for Clinical Practice who confirms that NICE should proceed to develop ESUOMs on those topics.

#### **Stage 5: Commissioning**

NICE sends the final list to the external supplier and formally asks them to develop an ESUOM for each topic.

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<sup>[3]</sup> Partner organisations are organisations with a particular interest in the unlicensed and off-label use of medicines. They include professional and patient bodies and trade organisations such as the Royal College of Paediatrics and Child Health, Rare Diseases UK, the Chief Pharmacists Network and the Association of the British Pharmaceutical Industry (ABPI). A list of partner organisations will be available on the NICE website, but is not intended to be exhaustive, as we aim to engage with all who can help identify potentially suitable topics.



## 5 Production

### 5.1 Equality and diversity considerations

ESUOMs are developed in accordance with the NICE equality scheme (available from <http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp>).

### 5.2 Process and timescales

ESUOMs are not formal NICE guidance and therefore are not subject to the same intensity of process as other NICE products.

The table below shows the key steps in the production of ESUOMs.

**Table 1: Key steps of production of an ESUOM with timelines**

| Key step  | Responsible party | Completed by |
|---|-------------------|--------------|
| <b>Topic selected and referred to supplier</b>                | NICE              | Week 0       |
| <b>Scope topic</b>  | Supplier          | Week 1       |
| <b>Contact manufacturer and/or regulator for data</b>         | NICE              | Week 1       |
| <b>Literature search</b>                                      | Supplier          | Week 1       |
| Searching for evidence  | Supplier          | Week 1       |
| Sifting and selecting the evidence                            |                   | Week 2       |
| Appraising and categorising the evidence                      |                   | Week 2       |
| <b>Authoring the ESUOM:</b><br>Produce initial draft of ESUOM | Supplier          | Week 4       |
| Preliminary technical check of initial draft by supplier      | Supplier          | Week 5       |

|  |          |         |
|--|----------|---------|
| <p><b>Review of draft ESUOM:</b></p> <p>Initial draft sent to manufacturers, regulators and specialist commentators for review</p> <p>Initial draft of summary for patients sent to Patient and Public Involvement Programme</p> | Supplier | Week 5  |
| Review comments received and revised draft produced  | Supplier | Week 7  |
| <p><b>Quality assurance of the ESUOM:</b></p> <p>Technical and editorial check of content by supplier</p>  | Supplier | Week 7  |
| Revised draft sent to NICE   | Supplier | Week 8  |
| Technical check of content by NICE senior adviser  | NICE     | Week 9  |
| Editorial check of content by NICE Editorial team  | NICE     | Week 10 |
| Final check of content by Medicines and Prescribing Programme Director   | NICE     | Week 10 |
| <p><b>Sign off and publication of the ESUOM:</b></p> <p>Guidance Executive sign off</p>  | NICE     | Week 11 |
| Inform manufacturer of date that ESUOM will be published   | NICE     | Week 11 |
| Publication on NICE website  | NICE     | Week 12 |

## 5.3 Scoping of individual topics

The Medicines and Prescribing Centre and the contracted external supplier meet to scope each ESUOM topic. The scoping confirms the following.

- Key contacts at the pharmaceutical manufacturer
- Key contacts at the Medicines and Healthcare products Regulatory Agency (MHRA) or European Medicines Agency (EMA), to obtain evidence held on file which is not confidential
- Specialist commentators (via the New Medicines Community of Practice and other existing NICE networks)

- Commentators for the summary for patients, in liaison with the NICE Patient and Public Involvement Programme
- Terms for a literature search to identify published clinical trial data that reflect the indication for the unlicensed or off-label medicine
- Arrangements for identifying:
  - regulatory status
  - relevant published trials, or other data on the unlicensed or off-label medicine
  - evidence of clinical effectiveness for the UOM in the condition under consideration
  - safety issues, encompassing key adverse drug reactions, precautions and contraindications providing an indication of frequency of the adverse effects where possible
  - incidence and prevalence of the condition, what treatment alternatives exist and an estimate of current drug usage
  - cost of the medicine and the cost of alternative treatment options.

## 5.4 Contacting the manufacturer and medicines regulator

NICE informs the manufacturer<sup>[4]</sup> of the medicine that an ESUOM is going to be produced and asks the manufacturer to provide data to support the production of the ESUOM.

The NICE also contacts the MHRA (or EMA, as appropriate) to ask them for any evidence they hold on file that is not confidential.

Both the manufacturer and the MHRA (or EMA) are sent the timelines for the production of the ESUOM, including the deadlines for receipt of data and the expected dates for comment on a draft of the summary.

## 5.5 Literature search

### 5.5.1 Searching for evidence

A literature search is produced by the contracted external supplier according to the agreed scope and strategy. The search strategy is documented and included in an appendix to the published ESUOM. Quality assurance for the search process is also documented.

### 5.5.2 Sifting and selecting the evidence

The contracted external supplier sifts the final set of search results using the title and abstract of each article, applying first exclusion and then inclusion criteria.

These criteria include the basic criteria as set out below:

#### **First sift**

This process removes evidence based on the following exclusion criteria:

- articles of poor relevance against search terms
- publication types that are out of scope:
- non-English language abstracts, or non-English language studies with English abstract
- conference abstracts
- Cochrane, or other review protocols
- articles without either abstract or full text available.

#### **Second sift**

This sift of evidence includes relevant primary research that addresses the use of the medicine within the defined indication under review. Where robust randomised controlled trials or systematic reviews are available, then they form the basis of the review. However, given the nature of the work, the best available evidence on which to produce the evidence summary may include evidence other than randomised controlled trials.

The contracted external supplier records the reasons for inclusion and non-inclusion based on the second sift, as well as a 'long list' of those studies that are excluded from the first sift.

### 5.5.3 Appraising and categorising the prioritised evidence

The contracted external supplier prioritises the evidence for critical appraisal and records the reasons for non-inclusion of evidence. The full text of the prioritised evidence is appraised using an assessment form suitable for the type of evidence, which is provided by NICE.

## 5.6 Authoring of the ESUOM

The contracted external supplier drafts the ESUOM using a standard template, which includes the following sections:

- Title and contents page
- Date and version control information
- Summary for healthcare professionals, including:
  - Regulatory status
  - Clear summary statements of the evidence
  - Summary of the relative risks, benefits, strength of evidence, regulatory status and typical treatment costs
- Details of the intervention, including:
  - General information about disease or condition, incidence/prevalence and overall survival rate
  - Alternative treatment options with links to relevant guidance/evidence

- Review of available evidence, with relative strengths and weaknesses of evidence for:
  - Efficacy
  - Safety
  - Regulatory status
  - Cost and comparative costs of alternative options
  - Current drug usage
- References
- Appendices:
  - Search strategy
  - Evidence selection process and criteria used to inform this
- Summary for patients

## 5.7 Review of the draft ESUOM

The contracted external supplier sends the draft ESUOM to the identified external specialist reviewers, the manufacturers and the drug regulators for review. The draft is also sent to the expert patients or commentators, from patient groups identified by the PPIP, to provide comments on the summary for patients.

Any comments received are recorded by the contracted external supplier and considered within the production of the revised draft. Actions are also recorded.

## 5.8 Quality assurance of the ESUOM

Initial quality assurance of the ESUOM is carried out by the contracted external supplier. This will involve a detailed check of all content, to ensure all sections of the document contain statements and conclusions that are fair and balanced. They must, accurately reflect the evidence reviewed and be substantiated by an explicit and appropriate source of evidence. This will be carried out to a checklist provided by NICE. A further check for clarity, grammar, spelling and style is also undertaken by the contracted external supplier. All drafts and any changes to drafts are recorded for audit purposes.

The revised draft is then sent to the Medicines and Prescribing Centre, who, in conjunction with the NICE Editorial team, review it and produce a final draft. Once sign-off is received from the Programme Director of the NICE Medicines and Prescribing Centre, NICE Guidance Executive reviews the ESUOM, and if appropriate, approves the ESUOM for publication, ensuring that due process has been followed in its development.

## 5.9 Publication of the ESUOM

The final ESUOM is uploaded and made available online through the Medicines and Prescribing Centre page of the NICE website.

The NICE Communications team develops a communications plan for the ESUOM, together with the Associate Director within the Medicines and Prescribing Centre, and is responsible for disseminating the ESUOM once it has been published.

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<sup>[4]</sup> For some unlicensed or off-label medicines, more than one manufacturer may be involved in the development of the drug. On these occasions, all relevant manufacturers based in the UK will be contacted for information.

## 6 *Review*

*The process for reviewing and updating ESUOMs will be considered as part of the consultation with key groups on the final process guide. In the meantime, the need to update published ESUOMs will be dealt with on an ad-hoc basis by the Medicines and Prescribing Centre at NICE.*



## **7 About this interim process statement**

*This interim process statement was used to develop evidence summaries: unlicensed and off-label medicines published up to 15 May 2013, but evidence summaries published after this date have used the [integrated process statement](#).*

*For published 'Evidence summaries: unlicensed and off-label medicines', see the [list](#) on the NICE website.*

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