



Healthcare  
Improvement  
Scotland

**SMC**  
Advice on new  
medicines

# Guidance to Submitting Companies for Completion of New Product Assessment Form (NPAF)

Supplement for medicines for extremely rare  
conditions (ultra-orphan medicines)

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**[www.scottishmedicines.org.uk](http://www.scottishmedicines.org.uk)**

# 1. Background

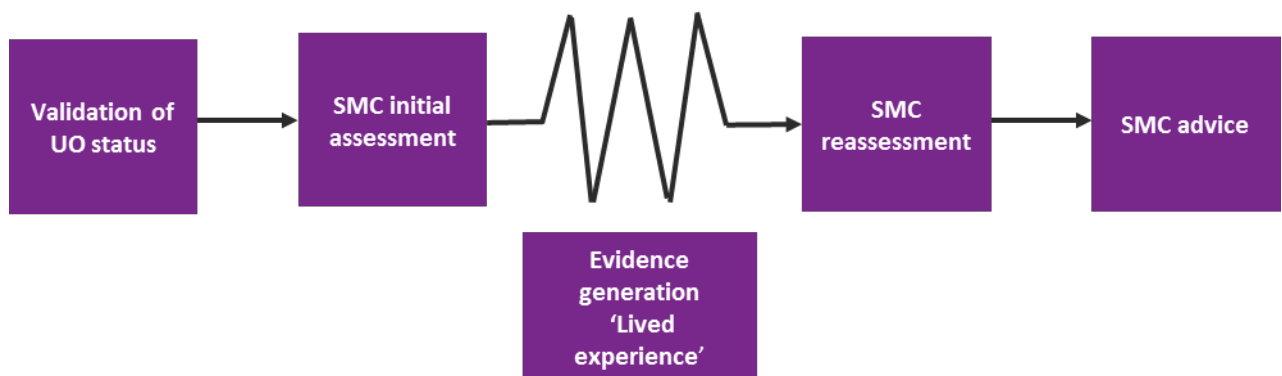
The Scottish Government published a [Review of Access to New Medicines](#) in December 2016. This recommended a new definition and pathway for medicines to treat extremely rare conditions (ultra-orphan medicines) in NHSScotland.

From April 2019, submissions for medicines that are validated as ultra-orphan according to the new definition will be assessed by SMC and will then be available to prescribers for a period of up to three years while further clinical effectiveness data are gathered. The company should then provide an updated submission for reassessment allowing SMC to make a decision on routine use of the medicine in NHSScotland.

The ultra-orphan pathway involves the following key stages:

- Validation of ultra-orphan status
- SMC initial assessment
- Evidence generation for a period of three years
- SMC reassessment followed by issue of advice to NHSScotland

Figure 1: Ultra-orphan pathway



Please refer to the appendix 2 for a more detailed diagram with timelines.

This supplement provides guidance for submitting companies on ultra-orphan validation, SMC initial assessment, and reassessment within the ultra-orphan pathway. It should be read in conjunction with SMC Guidance on completion of New Product Assessment Form (NPAF) available on the *Making a submission* section of the SMC website.

General guidance on the implementation of the ultra-orphan pathway is also available at <https://www.gov.scot/publications/ultra-orphan-medicine-pathways-guidance/>

## 2. SMC ultra-orphan definition (2018)

To be considered as an ultra-orphan medicine all criteria listed should be met:

1. The condition<sup>1</sup> has a prevalence of 1 in 50,000 or less in Scotland
2. The medicine has a European Medicines Agency (EMA) orphan designation for the condition and this is maintained at time of UK marketing authorisation
3. The condition is chronic and severely disabling
4. The condition requires highly specialised management<sup>2</sup>

<sup>1</sup>typically a recognised distinct disease or syndrome. SMC uses the description of the condition within the EMA's Orphan Maintenance Assessment Report (OMAR) as a reference (or the description within the original orphan designation if the OMAR is not available).

<sup>2</sup>for example, within the context of a nationally funded service.

## 3. Process for submissions for ultra-orphan medicines

### 3.1 Validation

Companies are encouraged to seek confirmation that a medicine meets the ultra-orphan definition at an early stage, and ideally prior to receiving a positive opinion from the EMA's Committee for Human Medicinal Products (CHMP), by completing the ultra-orphan proforma available on the *Making a submission* section of the SMC website.

The SMC Executive will review the proforma and will confirm whether the medicine has been validated as ultra-orphan within around eight weeks. The outcome of the ultra-orphan validation is shared with NHS Boards in confidence. If SMC validates a medicine before the EMA OMAR is available then ultra-orphan status is contingent on maintenance of EMA orphan designation at the time of marketing authorisation.

If the company disagrees with the outcome of the validation there is the opportunity to appeal. Further information is available on the *Policies and publications* area of the SMC website.

In addition to SMC ultra-orphan status, Scottish Government has outlined three further conditions which must be met to enable a medicine to enter the new pathway. The company is required to:

- Make a full submission to SMC to allow an initial assessment of clinical and cost effectiveness
- Offer a Patient Access Scheme (PAS) that complies with the standard terms and conditions considered acceptable by the Patient Access Scheme Assessment group (PASAG)
- Support data collection arrangements that meet evidence generation requirements for assessment under the ultra-orphan pathway

Confirmation of ultra-orphan status is required before the company makes a submission for SMC initial assessment (using the New Product Assessment Form for Ultra-Orphan Medicines).

After a medicine has been validated as an ultra-orphan, the company can request a meeting with SMC before making the initial submission. Further details on *Early engagement with companies* are available under the *Making a submission* section of the SMC website.

## 3.2 SMC initial assessment

An initial assessment of the clinical and cost-effectiveness of the medicine will be conducted. This will highlight uncertainties within the available evidence-base and will help to inform the data collection stage of the ultra-orphan pathway.

SMC will use a broad framework to assess ultra-orphan medicines which takes account of the following:

- Nature of the condition
- Impact of the medicine
- Value for money
- Impact of the technology beyond direct health benefits and on specialist services
- Costs to the NHS and Personal Services

### 3.2.1 Completion of the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines – SMC initial assessment

Companies should complete the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines available in the *Making a submission* section on the SMC website. This is structured to mirror the framework described above. This supplement provides companies with guidance on the additional information requirements for this group of medicines and should be used in conjunction with general SMC Guidance to submitting companies.

#### **Nature of the condition (Ultra-orphan NPAF section 3)**

This section should provide a description of the ultra-orphan disease or condition and its impact on patients and carers, including:

- Severity of the condition, symptoms, pattern of disease progression, level of disability, overall effect on morbidity and mortality.
- Effect on functioning e.g. ability to work, participate in education, self-care, undertake activities of daily living.
- Effect on the patient's quality of life and on family and carers' quality of life.
- Description of currently available treatment options. These may include disease-specific treatments and/or supportive therapies.

- Limitations of currently available treatments including side-effects, burden in terms of administration and monitoring, hospitalisation and clinic attendance.
- Level of unmet need in NHSScotland.

#### **Impact of the new technology (Ultra-orphan NPAF section 4)**

In addition to information on clinical efficacy, safety and clinical effectiveness, companies should consider:

- How outcomes from observational studies including disease registries or early access schemes could supplement conventional clinical study data.
- Effect of the medicine on patient experience and patient reported outcomes such as health-related quality of life, health status, physical functioning, activities of daily living, adherence to treatment, patient satisfaction with treatment etc.
- How the medicine would be expected to address any areas of unmet need.
- For the initial submission, identification of uncertainties or evidence gaps and how these might be addressed.

#### **Value for money (Ultra-orphan NPAF section 5)**

While SMC recognises the challenges in providing a robust economic evaluation for a medicine used to treat an extremely rare condition due to limitations in the data available, an economic evaluation to indicate the value for money is required.

SMC has a preference for a cost-utility analysis for such medicines, where appropriate and feasible, as this allows comparability with other medicines across the value for money spectrum. However, where an evaluation using quality adjusted life years (QALYs) is not feasible, SMC will accept cost-effectiveness analysis using appropriate natural outcome measures. Cost-consequence analysis may also be provided where the submitting company judges that there are multiple relevant outcomes not readily captured within a QALY based assessment or cost-effectiveness analysis using a single outcome measure. The company would be expected to provide supporting rationale for the approach taken. SMC appreciates that in some conditions the economic evaluation will have significant uncertainty, but an estimate of the likely costs and benefits is still required.

Given the nature of extremely rare conditions, submitting companies may also wish to provide a sensitivity analysis supporting the base case economic evaluation that adopts a wider perspective than the conventional NHS perspective. This will permit the evaluation to reflect wider costs and benefits relevant to the patient and their carer, such as out of pocket expenses, lost earnings and carer quality of life gains from the new treatment.

#### **Costs to the NHS and Personal Social Services (Ultra-orphan NPAF section 6)**

In addition to completion of a standardised Excel template to show an estimate of the NHS budget impact, companies should include an assessment of any significant budget impacts for any non-NHS organisations.

## **Impact beyond direct health benefits and on specialist services (Ultra-orphan NPAF section 7)**

This section should describe potential impact of the medicine other than clinical benefits, adverse effects and on health-related quality of life, this may include:

- Opportunity for patients to contribute to society, improve family functioning, continue in employment or education.
- Impact on carers' quality of life (e.g. using tools such as the Carer Experience Scale) and ability to work.
- Impact of adopting a wider perspective on the cost-effectiveness of the medicine (e.g. incorporating loss of earnings, carer disutility).
- Implications of the introduction of the new medicine on the NHS including staffing, infrastructure and training requirements.

### **3.2.2 Evaluation of medicines used to treat ultra-orphan conditions – SMC initial assessment**

#### **New Drugs Committee (NDC) meeting:**

The clinical and economic evidence to support an ultra-orphan medicine will be assessed by NDC before being considered by the SMC Committee. An economic evaluation on the value for money of the medicine remains a requirement, but with the flexibility in approach described in section 3.21 above. An ultra-orphan assessment report will be structured according to the ultra-orphan framework. Following review of the medicine by the NDC, the draft NDC assessment report will be shared with the submitting company and company comments invited for consideration by the SMC committee.

Following NDC the company has the opportunity to submit a new or revised PAS aimed at improving the cost-effectiveness of the medicine. Refer to section 6.15 of the SMC Guidance to submitting companies for details of updated analyses required within the company comments document.

A Patient and Clinician Engagement (PACE) meeting will not take place at the time of the initial assessment but will play an important role in the reassessment and decision-making post evidence generation.

#### **SMC meeting:**

SMC will review the information presented in the ultra-orphan framework, examining the nature of the condition, impact of the medicine, value for money, costs to the NHS, and impact beyond direct health benefits using the criteria set out above.

As part of the review process, SMC will also consider other sources of evidence to supplement the framework presented within the draft NDC assessment report, e.g. from clinical experts and Patient Group submissions. This will ensure the Committee has as complete a picture as possible of the condition and the potential impact of the medicine. At the initial assessment, SMC will appraise the evidence presented prior to the medicine

being made available for an initial period as part of the ultra-orphan pathway. SMC will not make a decision on use of the medicine at this point.

The SMC ultra-orphan assessment report will provide a critique of the evidence-base presented, including key limitations and uncertainties in the clinical and economic evidence to help inform data collection during the period of initial availability of the medicine. SMC will publish this document on its website within standard timelines.

### 3.3 Evidence generation

Data collection development can begin at an early stage in parallel with SMC initial assessment. Scottish Government guidance to support the evidence generation phase of the ultra-orphan pathway is available at <https://www.gov.scot/publications/ultra-orphan-medicine-pathways-guidance/>

### 3.4 SMC reassessment

#### 3.4.1 Completion of the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines – SMC reassessment

The company will be required to provide a full updated submission following the period of evidence generation. Companies should complete the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines available in the *Making a submission* section on the SMC website as outlined in section 3.21 above. Results of further controlled studies, observational, registry or other real world data gathered during initial availability of the medicine within the ultra-orphan pathway should be included in relevant sections of the NPAF to address uncertainties identified at the time of the initial assessment. The updated submission must be provided in line with standard SMC Guidance to submitting companies including the relevant comparator(s) and within the context of the current treatment pathway in NHSScotland at the time of reassessment.



### 3.4.2 Evaluation of medicines used to treat ultra-orphan conditions – SMC reassessment

#### NDC meeting:

The clinical and economic evidence to support an ultra-orphan medicine will be assessed by NDC before consideration by the SMC Committee. The draft NDC Detailed Advice Document (DAD) will be structured according to the ultra-orphan decision-making framework.

Following review of the medicine by the NDC, the draft NDC DAD will be shared with the submitting company and company comments invited for consideration by the SMC committee.

If the draft NDC advice is 'not recommended', the submitting company will be offered the opportunity to request a PACE meeting and/or to submit a new or revised PAS. Refer to the general guidance notes section of SMC Guidance to submitting companies for further information.

#### SMC meeting:

SMC will review the information presented in the decision-making framework, examining the nature of the condition, impact of the medicine, value for money, costs to the NHS, and impact beyond direct health benefits using the criteria set out above. SMC will also consider the additional evidence generated during the period of initial availability of the medicine within the ultra-orphan pathway.

As part of its review, SMC will assess the information the company has provided within the ultra-orphan NPAF as well as other sources of evidence to supplement the framework within the NDC DAD, e.g. from clinical experts, Patient Group submissions and, where relevant, the output from a PACE meeting. This will ensure SMC is provided with as complete a picture as possible of the relevant aspects upon which the final decision will be based.

The SMC decision options at reassessment include:

- Accepted for use
- Accepted for restricted use
- Not recommended

## 3.5 Patient access schemes (PAS)

Provision of a PAS to improve cost-effectiveness of the medicine is a condition of the ultra-orphan pathway specified by Scottish Government. The company may offer the PAS at the time of initial SMC submission or following NDC when submitting company comments. A PAS that is made at the time of initial submission may be revised post-NDC.

At the time of reassessment, where the updated submission includes a PAS, the submitting company must provide a new PAS application in line with PAS guidance (refer to NHSScotland PAS Guidance available on the *Making a submission* section of the SMC website). The company has the opportunity to propose a new or revised PAS post-NDC. If the medicine is accepted for use at the time of reassessment the updated PAS will come into effect.

In the event that the medicine is not recommended for use at reassessment, or due to non-submission, the previously established PAS would continue to be in effect for the minimum period specified in said PAS agreement.

### 1. Why has the SMC definition of an ultra-orphan medicine changed?

The definition in use since 2014 was considered to be too broad. The 2016 [Review of Access to New Medicines](#) recommended development of a new definition of ‘true ultra-orphan medicine’ to take account of low-volume, high-cost medicines for extremely rare conditions. The new definition is available on the *How we decide* section of the SMC website under *Revised process – ultra-orphan medicine for extremely rare conditions*.

Of note, the new definition is based on the prevalence of the condition rather than the target population described in the licensed indication. SMC will use the description of the condition within the EMA’s Orphan Maintenance Assessment Report (OMAR) as a reference. In addition, the condition must be chronic and severely disabling and require highly specialised management.

### 2. How will the company know if a medicine meets the new definition?

The company needs to submit an ultra-orphan proforma and have this validated by SMC **before** making a submission. A submission for initial assessment of an ultra-orphan medicine must be made using the New Product Assessment Form (NPAF) for ultra-orphan medicines. Both the ultra-orphan proforma and the ultra-orphan NPAF are available on the *Making a submission* section of the SMC website.

### 3. What if a company disagrees where a medicine is not validated as an ultra-orphan?

Companies have the opportunity to appeal if they do not agree with the validation decision as follows:

#### **Request to reconsider validation outcome**

The company should provide a short statement to explain the basis of the disagreement within three months of being notified of the validation outcome.

#### **Appeal process**

The appeal panel will consist of three members of the SMC executive who did not participate in the initial validation, including the SMC Chair. The panel will review the proforma initially

provided by the company to support ultra-orphan status, together with responses from clinical experts. No new data can be submitted as part of the appeal. Conflicts of interest will be handled in line with standard SMC arrangements.

### **Conclusion of appeal**

The appeal panel will reach a view on whether the medicine meets the ultra-orphan criteria. The company and NHS boards will be advised of the conclusion.

## **4. What if relevant new evidence becomes available to support validation for a medicine that was previously not validated as ultra-orphan?**

In the event that SMC does not validate a medicine as meeting the ultra-orphan criteria but relevant new information becomes available to support validation, the company has the opportunity to update the original proforma and resubmit to SMC. The information should be submitted using the ultra-orphan proforma available on the *Making a submission* section of the SMC website.

SMC Executive would then consider all the information provided according to our standard validation process and timelines before advising whether the medicine would now meet the new ultra-orphan definition.

## **5. What does the new ultra-orphan pathway involve?**

Within the new pathway, ultra-orphan medicines will undergo an initial SMC assessment of clinical and cost-effectiveness and will then be available for period of up to three years while further evidence is gathered to support SMC reassessment and a decision on routine use of the medicine in NHSScotland.

In addition to SMC ultra-orphan status and making a full submission to SMC, the company must also agree to provide a Patient Access Scheme (PAS) to improve cost effectiveness of the medicine, and to collect further data on clinical effectiveness over the initial period of availability of the medicine. If preferred, a company can choose to submit under the current orphan assessment process, with the opportunity for a Patient and Clinician Engagement (PACE) meeting. In addition, for medicines with EMA conditional marketing authorisation, SMC would also have the option of accepting the medicine for routine use on an interim basis. Please refer to *Guidance on submissions for medicines with EMA conditional marketing authorisation* on the *Making a submission* section of the SMC website.

## 6. Can a medicine that was previously not recommended by SMC now enter the new pathway?

Yes, medicines that were previously not recommended for routine use by SMC may now be considered for the new ultra-orphan pathway. The medicine will first need to be validated as an ultra-orphan according to the revised definition and the requirements outlined above must also be met.

## 7. What happens if the company does not make an updated submission for reassessment?

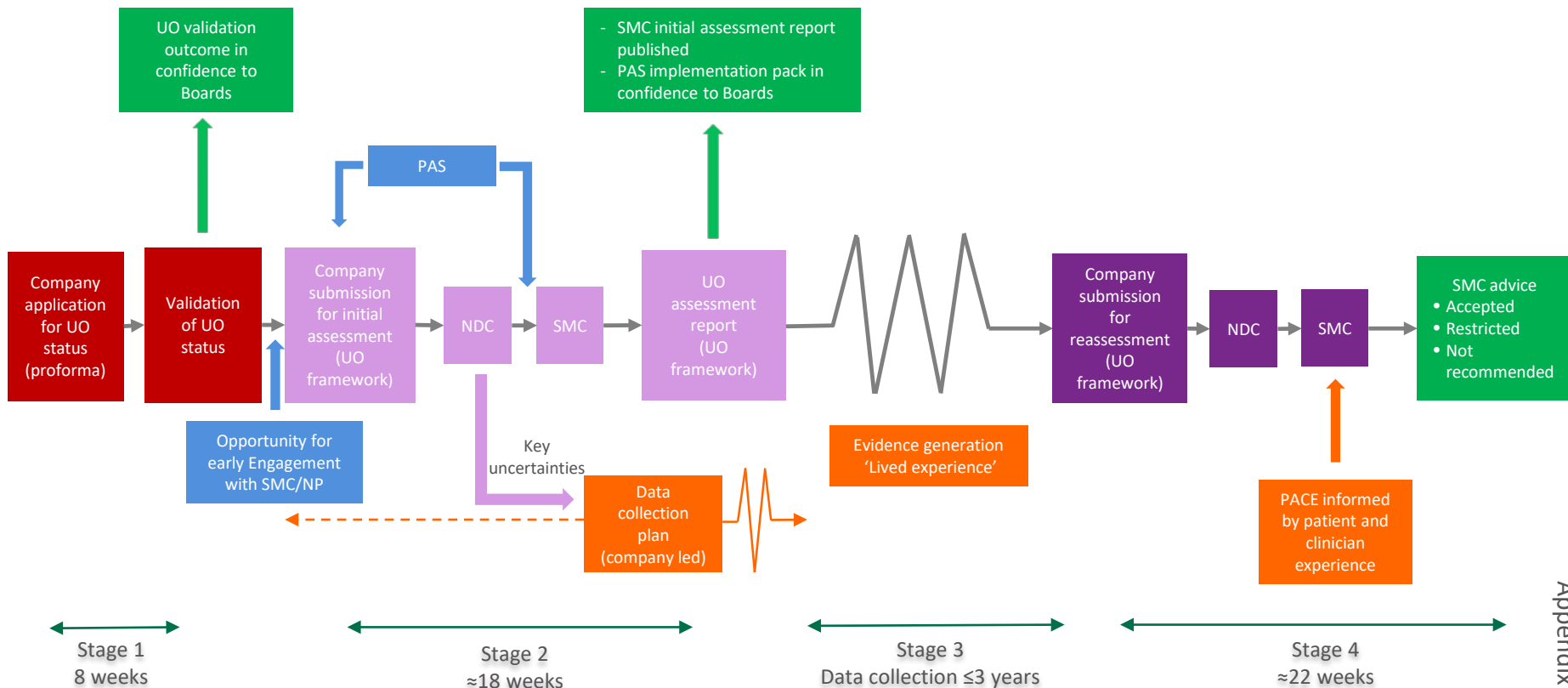
If the company does not provide an updated submission for reassessment following the period of data collection, SMC will issue not recommended advice.

## 8. What are the arrangements for existing patients if the medicine is not recommended on reassessment?

Where a patient continues to derive clinical benefit it is expected that they would remain on the medicine until the patient and clinician consider it appropriate to stop treatment.

# Ultra-Orphan Pathway

UO – ultra-orphan  
 PAS – Patient Access Scheme  
 NP – National Procurement  
 PACE – Patient and Clinician Engagement meeting



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