GUIDELINES ON CONDITIONAL REGISTRATION FOR NEW CHEMICAL ENTITIES AND BIOLOGICS

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National Pharmaceutical Regulatory Division
Ministry of Health Malaysia

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1.0 OBJECTIVES & SCOPE

The objective of conditional registration is to allow certain promising new medicines to reach patients with unmet medical needs earlier than the current framework while ensuring appropriate measures are in place to manage the risks inherent in the fact that the additional data are still required. This guideline provides guidance on the application necessary for implementation of conditional registration. It forms the basis for requesting or renewing a conditional registration and should be followed unless otherwise justified.

Certain new medicines can be conditionally registered on the basis of early clinical data such as Phase II clinical data to support the efficacy and safety. The data may be based on fully validated surrogate endpoints or other early data relevant to the medicine's safety and efficacy, rather than comprehensive data from Phase III clinical trials. Conditional registration applications must include comprehensive quality and non-clinical safety data that fulfil registration requirements as stated in the Drug Registration Guidance Document.

The possibility of obtaining a conditional registration only applies to new registration applications for new chemical entities and biologics. At the point of submission, the product must be registered in at least one Drug Control Authority (DCA) reference agencies. A conditional registration does not apply to additional indications submitted post-registration. Once a product has been granted a full registration that is not subjected to any specific conditions, the full registration approval cannot be reverted into a conditional registration approval. However, the approval of additional indication with less than comprehensive clinical data may be considered on case-to-case basis.

2.0 ACCEPTABILITY OF CONDITIONAL REGISTRATION REQUEST

A conditional registration may be requested by the product registration holder (PRH). The PRH is required to notify NPRA by writing formally about their request for a conditional registration

The request should consist of justifications as follows:

i) to show that the medicinal product falls within the scope of the conditional registration
ii) the requirements for conditional registration are fulfilled
iii) PRH's proposal for completion of ongoing or new studies, or the collection of pharmacovigilance data

i) Justification that the medicinal product falls within the scope of the conditional registration

The PRH should justify that the medicinal product falls within the scope of the conditional registration. The product should belong to at least one of the following categories:

a) Medicinal products for seriously debilitating diseases or life-threatening diseases

The severity of the disease, i.e., its seriously debilitating, or life-threatening nature needs to be justified, based on objective and quantifiable medical or epidemiologic information. Whereas a life-threatening disease is relatively easy to describe based on figures of mortality, justifying that a disease is seriously debilitating will have to consider morbidity and its consequences on patients' day-to-day functioning. These aspects should be quantified in objective terms, as far as possible. Furthermore, serious debilitation, or fatal outcome should be a prominent feature of the target disease and therapeutic indication.

b) Medicinal products to be used in emergency situations

A justification should be provided that the medicinal product is intended for use in emergency situations, in response to public health threats.

c) Orphan medicinal products

Decision by respective committee within the Ministry of Health on the designation as an orphan medicinal product should be provided.

ii) Fulfillment of the requirements for conditional registration

In its request for a conditional registration, the PRH should justify why in their opinion each of these requirements are expected to be met:

a) The risk-benefit balance of the product is positive

In general, the demonstration of a positive benefit-risk balance should be based on (comprehensive) scientific evidence, in particular evidence from therapeutic confirmatory trials that can provide the most clinically relevant and convincing evidence directly related to the primary objective of the trial (randomised controlled trials).

In particular, the design of clinical studies pertinent to the claimed indication should in general be controlled and steps should be taken to avoid bias, including methods of randomisation and blinding. As for any other type of registration, the design and choice of control of the confirmatory trials need to be justified, and should be adequate. However, if the benefit-risk balance is judged to be positive but based on less than comprehensive clinical data, this would lead to the granting of a conditional registration. It should be possible, and indeed required, to obtain comprehensive data once ongoing or new studies have been completed. The uncertainties related to the lack of comprehensive clinical data in a conditional registration generally require that uncertainty deriving from other parts of the application are kept to a minimum.

The safety profile of the medicinal product should be adequately defined and appropriate to justify a positive benefit risk.

b) It is likely that the PRH will be able to provide comprehensive data

The PRH who applied for a conditional registration shall be required to complete ongoing studies, or to conduct new studies, with a view to confirm that the risk-benefit balance is positive. In emergency situations, specific conditions to provide comprehensive non-clinical or pharmaceutical data may also be required.

Comprehensive data are intended to confirm that the benefit risk balance is positive, for instance, by checking the coherence of the available data on primary or secondary endpoints in more mature data sets or in additional studies in related indications, investigating the effect duration, and generally providing a better estimate of the efficacy and safety of the product.

Specific conditions should aim to obtain evidence that has a consequence on confirming the benefit-risk in the approved indication. The PRH should explain how the comprehensive data can be provided post-registration.

For each on-going or new study that is proposed to be provided as part of a specific condition, a brief description should be provided.

c) Fulfillment of unmet medical need

One of the requirements for granting of a conditional registration is that unmet medical needs will be fulfilled. Unmet medical need is defined as a condition for which there currently exists no satisfactory method of diagnosis, prevention or treatment in the community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.

To address this requirement, PRH should justify that there exists an unmet medical need and that it is necessary to introduce new methods in therapy when no methods exist, or that it is necessary to provide a major improvement on the existing methods. The demonstration of fulfillment of an unmet medical need has to be justified on a case-by-case basis. The justifications should quantify the unmet medical need based on quantifiable medical or epidemiologic data.

In general, for a full registration, major therapeutic advantage would normally be based on meaningful improvement of efficacy (or clinical safety), such as having an impact on the onset and duration of the disease condition, or improving the morbidity or mortality of the disease.

The advantages should be demonstrated over existing methods used in clinical practice (if any), using robust evidence, normally, from well conducted randomised controlled trials (evidence-based demonstration of benefit).

For a conditional registration, in order to support the claim that unmet medical needs will be fulfilled, the PRH will be expected to provide:

- A critical review of available methods of prevention, medical diagnosis or treatment, highlighting an unmet medical need

- Quantification of the unmet medical need taking into account technical argumentation (e.g., quantifiable medical or epidemiologic data)

- A justification of the extent to which the medicinal product addresses the unmet medical need

d) The benefits of immediate availability to public health outweighs the risk of less comprehensive data than normally required, based on registration requirements

The PRH will have to provide a justification to substantiate the claim that the benefits to public health of the immediate availability of the medicinal product outweigh the risks inherent in the fact that additional data are still required. The justification should assess the impact of immediate availability on public health, based as far as possible on objective and quantifiable epidemiological information, as opposed to availability when comprehensive clinical data are expected to be available. Similarly, the risks inherent in the fact that additional data are still required shall be quantified as far as possible on objective and quantifiable terms.

In order to support the claim that the benefits to public health outweigh the risks inherent in the fact that additional data are still required, the PRH will have to provide a justification addressing the following points:

- Benefits to public health of the immediate availability on the market

- Risks inherent in the fact that additional data are still required

- How the benefits to public health in the context of immediate availability outweigh the risks (also taking into account the remaining questions)

iii) PRH's proposal for completion of ongoing or new studies, or the collection of pharmacovigilance data.

The PRH should state the proposal of completion of studies, or the collection of any pharmacovigilance data.

3.0 NPRA ASSESSMENT OF CONDITIONAL REGISTRATION

i) Granting of conditional registration

The decision whether to grant conditional registration or not will only be determined after thorough assessment has been completed and satisfactory feedback has been received by the PRHs.

In the event where the DCA is of the opinion that any of the requirement for the granting of a conditional registration is not fulfilled, and where the data provided in the application are considered insufficient to establish a positive benefit-risk balance, this would lead to a possibility towards not granting of a registration.

Upon granting conditional registration, the specific conditions will be clearly specified as follows but not limited to:

a) To submit data based on confirmatory trial/s or other trials that verify the predicted clinical benefit, where applicable
b) To implement Risk Management Plan based on the submitted plan including conducting enhanced post-market surveillance and reporting
c) To submit Periodic Benefit-Risk Evaluation Report (PBRER) and
d) Other conditions as stipulated by the DCA (if any)

As for all medicines, the NPRA will consider, on a case-by-case basis, the need for PRHs of conditionally registered products to undertake additional risk minimisation measures and communication activities as part of specific conditions to be implemented in post marketing setting. These may include patient and/or health professional education, Dear Healthcare Professional letters, limitations on which health professionals can prescribe the product or establishing a patient registry in certain circumstances.These commitments will be detailed in the Risk Management Plan.

Additionally, the package insert and package information leaflet (where applicable) for conditionally registered product will contain a statement that the product or specific indication, is conditionally registered and continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The example of the statement is as below. Any other statement that carries similar meaning may be also acceptable.

This indication is approved under conditional registration which is based on <surrogate/intermediate endpoint>

Continued approval for this indication may be based on the outcome of clinical benefit in a confirmatory trial

ii) Periodic Safety Update Reports/Periodic Benefit Risk Evaluation (PSUR/PBRER) or other equivalent safety update reports

PSUR/PBRER or other equivalent safety update reports shall be submitted to the NPRA immediately upon request or at least every six months following the granting or renewal of a conditional registration. Such requirement will be included as part of the registration conditions.

iii) Timeline for registration process

The timeline for conditional registration will follow a standard evaluation timeline for new chemical entities and biologics applications. However, in line with the objective of the conditional registration to facilitate earlier access to vital medicines, priority review may be considered upon request based on justification provided by the PRHs.

4.0 RENEWAL OF CONDITIONAL REGISTRATION

A conditional registration is valid for two years. Thereafter, the conditional registration may be renewed 2 times (with the possibility of 2 extensions of 2 years each).

i) Date for renewal

The PRH shall apply for its renewal at least six months before its expiry and shall provide the NPRA with an interim report on the fulfillment of the specific conditions through variation application.

NPRA will assess the renewal application on the basis of the risk-benefit balance and formulate an opinion whether the specific conditions or their timeframes need to be retained or modified.

ii) Documents to be submitted

General requirements

In order to allow the NPRA to confirm the risk-benefit balance of the medicinal product and to review the specific conditions and their timeframes for completion, the PRH should provide at least the following information in their variation application prior to renewal:

a) Package Insert
b) An interim or full clinical study report on the confirmatory trial, including clinical overview and relevant reference(s) (published paper) if any
c) Periodic Safety Update Reports/Periodic Benefit Risk Evaluation (PSUR/PBRER) or other equivalent safety update reports
d) Fulfillment on other conditions (if any)

5.0 FULL REGISTRATION

At any time, when the specific conditions have been fulfilled, NPRA may recommend the granting of a full registration at the time of renewal of the conditional registration or at the time of assessment of the data submitted to fulfill the specific condition(s).

6.0 CANCELLATION OF CONDITIONAL REGISTRATION

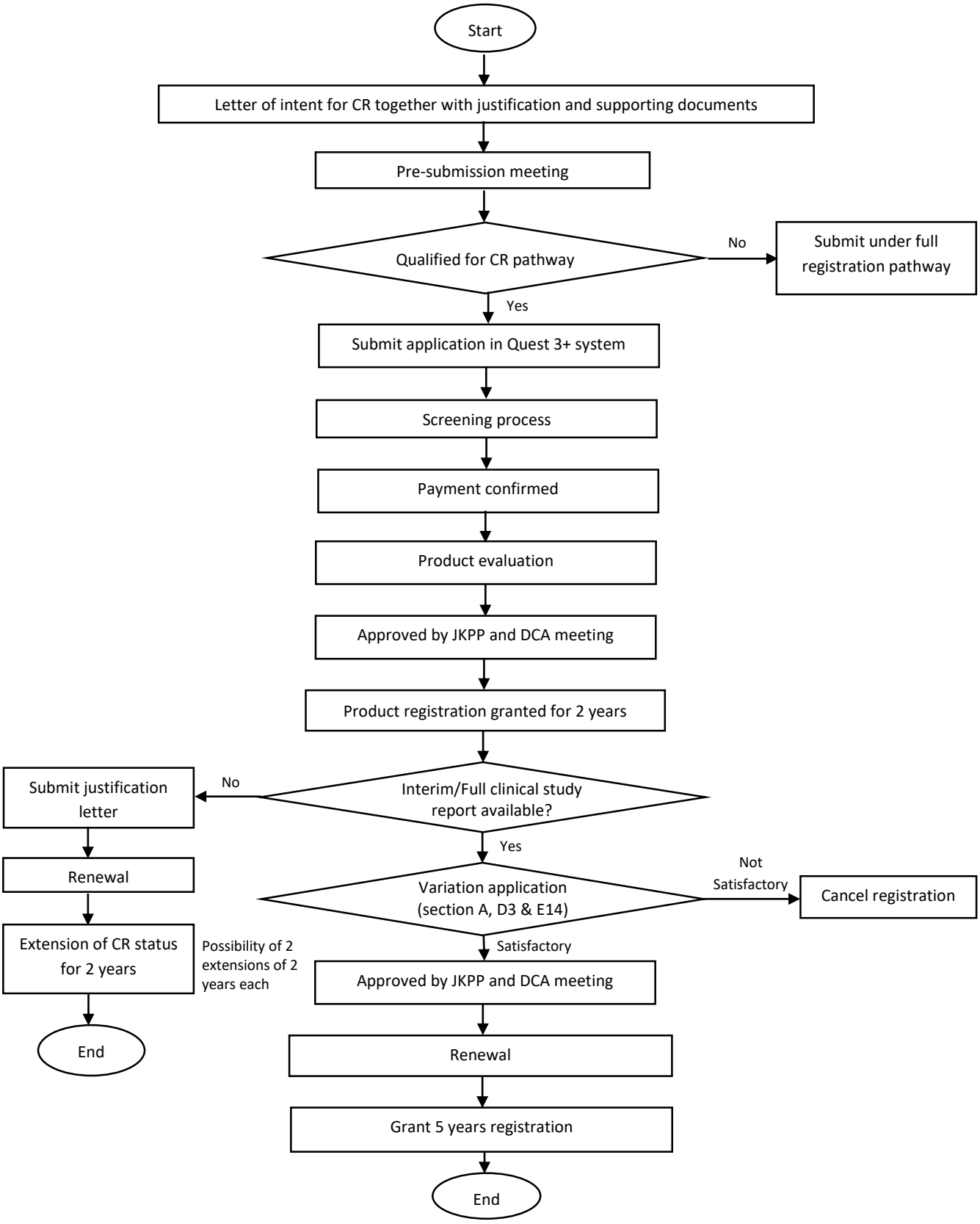
DCA may cancel the conditional registration of a product or cancel the approved indication under the conditional registration if:

i) A trial required to verify the predicted clinical benefit of the product fails to verify such benefit
ii) Other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use

7.0 DRUG CONTROL AUTHORITY RIGHTS

Notwithstanding the requirements stipulated in this guideline, DCA reserves the rights to use its own discretion whichever it deems fit.

8.0. FLOWCHART OF CONDITIONAL REGISTRATION (CR) PROCESS



9.0. REFERENCES

Adapted from the:

1. Guideline on the Scientific Application and the Practical Arrangements Necessary to Implement Commission Regulation (EC) No 507/2006 on the Conditional Marketing Authorisation for Medicinal Product for Human Use Falling Within the Scope of Regulation (EC) No 726/2004. EMA/CHMP/509951/2006, Rev.1 *25 February 2016*

2. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, U.S. Department of Health and Human Services Food and Drug Administration. *May 2014*

3. Guidance Document Notice of Compliance with Conditions (NOC/c)-Health Canada. *16 Sept 2016*