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Technical and Safety Improvement Section
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30 April 2018

Dear Sir/Madam,

Consultation: Management and communication of medicines shortages

Please find attached the response from Novartis Pharmaceuticals Australia Pty Ltd ['Novartis'] on the TGA public consultation paper on the proposed changes to the management and communication of medicines shortages.

Sandoz Pty Ltd is a related company of Novartis and is a global leader in the development and supply of generic and biosimilar medicines. This experience has helped to guide the comments and recommendation in this submission.

Whilst Novartis did support the current voluntary reporting system and promptly provided the TGA with information on all shortages of its medicines, we understand that the existing model has a number of shortcomings as noted in the consultation paper. Novartis now accepts the proposed new requirement for mandatory reporting of all shortages to the TGA in confidence, and only those shortages deemed to be of 'extreme' or 'high' patient impact would be mandatorily published on the TGA's website.

In this submission, we respond to the four consultation issues in the consultation paper giving consideration to the specific questions posed by the TGA for each issue. In addition, we have made additional comments towards the end of our submission to which we would request responses from the TGA.

Responses to consultation issues

Consultation issue 1: The definition of a medicine shortage

Novartis' response to this issue is mainly in relation to the proposed definitions of a medicine shortage and specifically the definitions for (b) the 'partial availability' of a medicine from the

sponsor, wholesaler or manufacturer; and (c) 'other constraints' on the medicine's availability. We also have some questions regarding the proposed scope for covered medicines.

Partial availability

Within the proposed definition of a medicine shortage, (b) partial availability is not defined. We presume it is intended to cover situations where the demand for a medicine is not fully met by adequate supply. Nonetheless, it remains unclear at what point a sponsor will need to take action in these instances in order to meet the reporting obligations suggested by the TGA for reporting a medicine shortage due to the range of causes and contributing factors that combine to create the shortage. The following theoretical example is provided here to illustrate the point:

> *Assume Company A supplies an innovator product (Product A). Another company (Company B) makes a generic equivalent of this product (Product B). Company A has 30% of the market share (Product A) and Company B has 70% of market share (Product B) for this product. If the amount of Product B supplied declines, and manufacturing of Product A cannot be ramped up within a sufficient time period to cover patient demand (consequently demand of Product A increases), would the sponsors of both Product A and Product B need to notify the TGA of the shortage of the medicine, or only the sponsor of Product B?*

Other constraints

We request that the TGA clarify what it envisages as being examples of (c) other constraints on the medicine's availability that are not adequately covered by (a) the unavailability of a medicine from a sponsor, wholesaler or manufacturer or (b) the partial availability of a medicine from the sponsor, wholesaler or manufacturer. If this is considered to be required, will the TGA also consider expanding the powers under section 19A of the Therapeutic Goods Act 1989 to also cover these types of scenarios? Currently section 19A is only available in circumstances whereby a medicine is unavailable or in short supply (partially available).

Proposed scope for covered medicines

Prescription medicines and a small number of non-prescription medicines are proposed to be within scope of medicine shortages reporting. Novartis requests that the TGA confirm if Prescription Medicines covers Schedule 4 (Prescription Only Medicines) and Schedule 8 (Controlled Drug) products.

We would also request that the TGA clarify whether kits and composite packs are in scope of the proposed definition for a medicine shortage.

Consultation issue 2: Reporting obligations

Novartis agrees that all medicine shortages should be reported by the sponsor to the TGA as soon as practicable after becoming aware of it and sees no issue with reporting a shortage within the suggested timeframes for anticipated and current shortages. We acknowledge and support the

proposal that only those shortages of medicines on the TGA's proposed 'medicine watch list' and deemed to be of 'extreme' or 'high' patient impact should be mandatorily published on the TGA's website.

We see no reason that discontinuations could not be reported in a similarly timely manner as an anticipated shortage and as soon as practicable after the sponsor becomes aware. **However, Novartis is deeply concerned over how sponsors will be able to meet the reporting obligations for the suggested lead times in those situations where they are not able to anticipate a discontinuation (eg. due to quality issues or manufacturing problems at an overseas site) and where continued supply of the product may also place patients at unnecessary risk.**

Comments on the suggested timeframes for anticipated and current shortages

Novartis supports the proposed timeframes for sponsors to report an anticipated and current medicine shortages. There may be instances where it may not be possible for sponsors to provide an estimate of the duration within the proposed 2 business day timeframe if, for instance, the shortage also affects supply of the medicine in other countries and there is a need to reevaluate worldwide forecasting before a sponsor can give a reliable estimate to the TGA. Whilst this should not prevent a sponsor from notifying the TGA of the actual shortage within the proposed 2 business day timeframe (thus, meeting its compliance obligations), Novartis recommends that the TGA allow sponsors more time to provide a reliable estimate of the duration of the shortage to reduce the risk of stock-piling of products and/or increase the shortage of alternative products. This may involve discussions with multiple stakeholders, often manufacturing sites outside of sponsor parent company, which adds to the complexity and time it may take to provide a reliable estimate of the expected duration of a shortage. Depending on the reason for disruption in supply or shortage (eg. permanent discontinuation, quality issue, safety issue,), we believe it will be difficult for a sponsor to unfailingly meet the proposed reporting period.

Comments on the suggested lead times for notifying a discontinuation

Novartis is concerned with applying fixed lead times to report a discontinuation, in particular the 12 month lead time for reporting a discontinuation of a medicine with extreme/high patient impact. With the exception of those instances where a company decides to stop making a medicine where alternative therapeutic options exists, discontinuations due to unanticipated difficulties with manufacture, or persistent quality problems (especially if these occur at an overseas manufacturing site) are generally beyond the Australian sponsor's control and the timeframes will vary depending on the circumstances.

Other situations that may also compel sponsors to discontinue medicines include PBS price disclosure related changes to business strategy. In this event, the company may not be in a position to allow for a 12 month notice period, depending on the timing of advice from the Pharmaceutical Benefits Pricing and Policy Branch.

Discontinuations due to quality reasons will usually impact worldwide supply of a medicine. However, we note that the timing proposed by the TGA for reporting a discontinuation of extreme/high impact appear to be considerably longer than the timeframes required by the EMA, FDA and Health Canada. In the EU for instance, Member States must notify the competent authority within two months of a temporary or permanent interruption in supply:

> *"Article 23a of EMA Directive 2001/83 as amended:*
> *If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made* ***no less than two months before*** *the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the competent authority of the reasons for such action in accordance with Article 123(2)."*[1]

The FDA requires that manufacturers notify the Agency **at least six months** prior to discontinuing manufacture of a medicine. Interestingly, the six month period mandated by the FDA may be shortened if the FDA finds "good cause" exists for sending a notification within a shorter timeframe, for instance if continuing to manufacture results in a public health problem or exposes the manufacturer to additional liability[2]. Health Canada also require manufacturers to post a shortage report **at least six months before** the shortage is anticipated to begin[3].

Whilst Novartis accepts that early identification of an alternative medicine in cases of an extreme/high patient impact shortage is paramount, we believe it would be impractical to impose a longer lead time for reporting discontinuations in Australia than the EU, the US and Canada, and that doing so would place Australian sponsors at undue risk of non-compliance. **In keeping with the TGA's objective of revising the MSII Protocol to bring Australia into alignment with other major English-speaking countries, we strongly recommend that the timing for sponsors to report a discontinuation? should be no longer than those imposed by health authorities in these countries, ie. six months.** Even so, where the reason is due to unanticipated quality issues, the timing of the discontinuation may not be known far enough in advance to meet the timings suggested by the TGA. We would therefore urge the TGA that in these instances, it considers introducing appropriate exemptions to its planned legislative changes to allow a sponsor the opportunity to provide an appropriate justification for not reporting a discontinuation far enough in advance of the suggested lead time.

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[1] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[2] https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm079936.pdf

[3] https://www.canada.ca/en/public-health/services/publications/drugs-health-products/reporting-drug-shortages-discontinuations.html#5.3

Comments on the notification content

The notification content should also collect information on the following:

- Route of administration: Active ingredients contained within a dosage form can sometimes be administered through various routes of administration. These routes of administration are sometimes associated with different indications. Therefore, the route of administration should be reported in order to assist with the determination of the potential public health impact. This is acknowledged in the Medicines Watch List, which specifies the route of administration for some active ingredients (e.g., Vancomycin IV), however not for others (eg. tobramycin is used IV as well as a powder for inhalation).

- Proposed regulatory action(s) (if any): this would allow the sponsor to indicate any proposed regulatory action in order to mitigate or avoid the impact of the shortage, or the existence of an actual shortage. For example, this could be used by sponsors to flag and by TGA to prioritize related section 14 requests or Category 3 applications.

- Market Share: this can be used to determine the potential impact of the medicine shortage and the appropriateness of a section 19A application.

Consultation issue 3: Medicines Watch List (MWL) defining an 'extreme' risk shortage

Assessment/verification before publishing shortages of medicine on the MWL

Novartis supports a specific watch list of known critical medicines. However, we do have certain misgivings with the notion that the TGA will automatically publish all reported shortages of products containing these medicines. A shortage of a brand of a medicine – even one that appears on the MWL – may not necessarily have an impact on patients if other brands of the same medicine are readily available to meet the demand.

Publishing "automatically" implies that an assessment or verification of the true impact on Australian patients will not be made beforehand. Our concern is that such indiscriminate action will cause unnecessary alarm and stockpiling of critical medicines. We therefore ask that the TGA clarify and confirm that it will, in practice, undertake an initial assessment of the impact of all shortages - including shortages of medicines on the MWL - together with the sponsor and other stakeholders before a decision is made on whether to publish on the TGA website.

Maintenance of the MWL

When the TGA proposes to add/remove a medicine on the MWL, the rationale for the inclusion/removal should be provided to sponsors of those medicine(s) on the ARTG as well as clinical expert groups, with an opportunity provided for comment. If after considering comments, the inclusion is supported by the TGA, the updated list should be publically available on the TGA Medicine Shortages website. External stakeholders should be allowed to register to receive an RSS feed with any updates to the list (additions/removals).

We note as well that there are certain active ingredients on the Medicines Watch List that do not specify the route of administration. Whilst we believe that this is intentional for some ingredients, particularly those where there is only one route of administration, there are others with multiple routes of administration of which only some would be considered to have an 'extreme' or 'high' patient impact, if in shortage. For example, we believe that only the intravenous form (IV) of Tobramycin should be on the MWL.

As clinical practice evolves and other medicines are used in an emergency setting in preference to others that may be on the MWL. We therefore recommend that the TGA include a mechanism to periodically review or allow sponsors to propose changes to the list. We would request that the TGA also advise if alternatives to medicines that, if in shortage, would be deemed to have an 'extreme' or 'high' impact to patients, could be made available through section 18A (medicine stockpile in emergency situations) of the Therapeutic Goods Act 1989.

Consultation issue 4: Compliance obligations and potential penalties

As we mentioned above in our response to consultation issue 2 – reporting obligations, Novartis considers there to be little risk of not being able to comply with the proposed timelines for reporting anticipated or current shortages. However, Novartis believes that the timelines proposed for discontinuation (if these are adopted) will be difficult to meet in some circumstances (e.g., discontinuation of a medicine with extreme/high patient impact due to manufacturing/quality issues). Therefore, Novartis would be in favour of option 1 ('name and shame') over option 2 or 3.

It is unclear why Australia would need more severe penalties for non-compliance with mandatory reporting requirements than the US. The consultation paper makes the comment that the 'name and shame' policy provides a much greater incentive for compliance in a US context than it would in Australia due to the large size of the local US pharmaceutical manufacturing industry. It is not clear how this follows as the issue in question is compliance with reporting obligations, and the "shaming" would not be around shortages themselves (ie. perhaps as a result of manufacturing issues) but a failure to report on them. If a 'name and shame' system has worked well in the US, Novartis cannot see any reason why such a system would not also work in Australia.

If the government is nonetheless minded to impose financial penalties for non-compliance, Novartis is of the view that such penalties should be reserved only for cases where there is a deliberate breach or involving repeat offenders. In any event, Novartis would only support civil and criminal liability (Options 2 and 3) if all stakeholders can agree on a clear and unambiguous definition of Medicine Shortage, with explicit and reasonable exemptions to protect sponsors against such action when shortages are unanticipated and outside of their control, and then only for medicines on the Medicine Watch List (or where the unavailability is likely to have an extreme or high patient impact).

Other comments and requests for clarification

Communications about confirmed shortages

Novartis understands that the TGA will publish all shortages of extreme or high patient impact on its TGA website. Novartis would request that the TGA clarify under what circumstances it may direct a sponsor to issue any additional communications to stakeholders.

Substituting an existing product with a therapeutic equivalent

From time to time, a sponsor may decide to phase out one of its existing products and substitute it with a newly registered bioequivalent or therapeutically equivalent form of the product containing the same pharmaceutical ingredient. We would assume that as long as patients who are currently on the existing form of the product can safely and effectively be transitioned to the new product there should be no need for the sponsor to notify the TGA of its decision to discontinue the existing product.

Potential role for prescribing and dispensing software vendors in the communication of shortages

Novartis believes there is value to be gained by health practitioners, patients and the public health system more broadly if the TGA engages and works with prescribing and dispensing software vendors as well as clinical expert groups to integrate medicine shortage notifications and recommended alternative treatment options in prescribing and dispensing software.

Concluding remarks

In summary, Novartis accepts the proposed new requirement for mandatory reporting of all shortages to the TGA in confidence, and only those shortages deemed to be of 'extreme' or 'high' patient impact would be mandatorily published on the TGA's website. Novartis accepts the proposed timeframes for sponsors to report an anticipated and current medicine shortage, provided the TGA allows sponsors more time to give a reliable estimate of the duration of the shortage to reduce the risk of stock-piling of products and/or increase the shortage of alternative products.

Novartis is concerned with applying fixed lead times to report a discontinuation, in particular the 12 month lead time for reporting a discontinuation of a medicine with extreme/high patient impact. The proposed 12 month lead time is also not consistent with the practices of EMA, FDA and Health Canada. For this reason, we would object to longer than a six month lead time for reporting an anticipated discontinuation, which is consistent with the requirements of comparable overseas regulators such as the FDA and Health Canada. Importantly, sponsors should not be held accountable for any discontinuation that is beyond their control (for instance, due to unanticipated quality problems at an overseas manufacturing site) and appropriate exemptions should also be put in place in Australia to manage such situations in a fair and reasonable manner.

Novartis is in favour of publicly identifying non-compliant sponsors, without additional sanction (Option 1) as the system has worked well in the US and there should be no reason why such a system would not also work in Australia. In addition, Novartis would urge the TGA to work with prescribing

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and dispensing software vendors as well as clinical expert groups to integrate medicine shortage notifications and recommended alternative treatment options in prescribing and dispensing software.

Novartis thanks the TGA for considering its submission.

Yours sincerely,

[redacted]

Lillis George

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