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28 May 2013

IVD Stream
Devices Conformity Assessment Section
Office of Devices Authorisation
Therapeutic Goods Administration
WODEN ACT 2606

Dear IVD Stream,

RE: Proposed Amendments to the New Regulatory Framework for IVDs

We are pleased to provide comments on the above consultation.

Alere is a healthcare/health management organisation and to achieve our goals we market a range of *in vitro* diagnostic products with a focus on professional point of care (POC) and home use testing. The company has considerable experience with diagnostic testing both from a technical and clinical outcomes perspective.

We appreciate the opportunity to provide feedback on this consultation. If you have any questions regarding the comments or if additional information would be useful please do not hesitate to contact me: mark.volling@alere.com

Yours Sincerely,

Mark Volling

Managing Director, Alere

Issue 1: Timeframe for valid applications for inclusion in the ARTG

Alere considers that "*Proposal 1A, A staged transition to the new IVD framework*." is reasonable and appropriate.

Although the 4 year transition period would appear, on first inspection, to be sufficient to ensure that manufacturers obtain conformity assessment certificates for their Class 4 IVD products, in practice this has not been the case.

Alere understands that there is a significant backlog of conformity assessments that are currently under review by the TGA and there is some concern that the TGA will not be able to complete the assessments by the June 2014 deadline, potentially leading to disruption to supply of critical Class 4 IVDs.

The proposal to change the June 2014 requirement for Class 4 IVDs from a valid inclusion application to a valid TGA conformity assessment application is supported. It is considered that this will provide sufficient time for manufacturers to submit valid applications.

The revised deadline of June 2015 for a valid inclusion application for Class 4 IVDs is also supported on the provision that the TGA ensures sufficient resources are available for the timely completion of conformity assessments prior to this deadline.

Alere considers that if the revised deadline is adopted then Class 2 and 3 IVDs manufactured in Australia and all Class 4 inclusion entries should not be charged annual fees until the June 2015 deadline. This will ensure that manufacturers/sponsors who have submitted valid inclusion applications by the original deadline are not penalised by this change in timelines.

Issue 2: Regulatory Requirements for Class 4 In-House IVDs

Alere considers that "*Proposal 2A, A modified conformity assessment procedure for the regulation of Class 4 in-house IVDs predicated on commercial IVDs.*" is overall a reasonable compromise between protecting patient safety by ensuring high quality IVDs and the practical challenges presented by some relatively low volume tests such as those which use cadaveric samples.

By definition, Class 4 IVDs are products that represent a high level of risk to public health if they do not perform adequately. These IVDs are essential in ensuring the blood supply and organ donations are safe, and that serious infectious diseases are diagnosed correctly.

These critical IVDs should be subject to the same level of premarket review to ensure that they have appropriate performance and quality, regardless of whether they are manufactured by a commercial manufacturer or in-house by a medical testing laboratory.

However, the points raised in the consultation document regarding in-house IVDs that are predicated on commercial IVDs are valid. Namely:

- It would generally be difficult for a laboratory to supply complete manufacturing information for an in-house IVD based on a commercial IVD.
- Where a commercial IVD has already been reviewed before being placed on the ARTG it does not make sense to re-review this complete set of data when a minor change has been made in-house.

Overall, the changes that are considered not to be fundamental changes to the IVD, i.e. changes that would be suitable for a modified conformity assessment procedure, are reasonable with the exception of "*the use of a Class 3 IVD for donor screening when a class 4 IVD is not available*".

If such a provision is adopted generally there would be strong disincentive for commercial manufacturers to develop and commit the resources required to validate Class 4 IVDs for supplemental or additional donor screening because laboratories could simply adapt in-house a Class 3 IVD.

Malaria is provided as an example of a potential test where a Class 3 IVD could be adapted for donor screening. However, approximately 50,000 blood donations a year (4.6% of total donations) are screened for malaria each year (Seed *et al.* 2009).

It is considered that the change from a Class 3 malaria IVD intended to aid in the diagnosis of malaria in symptomatic patients to a Class 4 malaria IVD intended for large scale supplemental screening of the blood supply is a fundamental change and would require a full conformity assessment. A Class 3 IVD needs to balance sensitivity and specificity in determination of its cut-off, whereas donor screening requires an emphasis on sensitivity to avoid false negative results and minimise the risk of transmission of infection. Modifying the balance of these analytical parameters would be a substantial modification and require comprehensive evaluation.

IVDs intended for routine supplemental donor screening should undergo a full conformity assessment process to ensure that their performance is sufficient to protect patient safety.

It is recognised that it may not be possible or practical for all non-routine donor screening tests to undergo a complete conformity assessment. As such, an abridged conformity assessment for a Class 4 in-house IVD predicated on a Class 3 IVD would be appropriate when no commercial Class 4 IVD is available on the ARTG.

Alere considers that "*Proposal 2B, A modified conformity assessment procedure for the regulation of all Class 4 in-house IVDs"* is not appropriate. The proposal would:

- Implement a two-tiered system for ensuring the quality and performance of these critical IVDs depending on whether they are manufactured in-house or by a commercial manufacturer.

  We have concerns that GMP and/or NATA auditors will not have sufficient resources to ensure that Class 4 in-house IVDs are manufactured and validated appropriately. Over one year is generally required for the TGA to perform a design examination and quality management system assessment. It is unclear how such a rigorous assessment can be compressed into a 2 or even 4 day GMP/NATA audit. Such reduced assessment would provide less assurance that these critical IVDs are sufficiently safe.
- Reduce transparency for all stakeholders because in-house IVDs would not be required to be entered on the ARTG. This is especially pertinent given that it is likely that TGA

decisions regarding conformity assessments and inclusion applications will be published in the future. Patients and end-users could potentially have no information on why an in-house Class 4 IVD is considered to be safe and effective compared to a published decision for a commercial IVD.

- Be a significant disincentive for commercial manufacturers to develop Class 4 IVDs for the Australian market because of much greater regulatory burden and fees compared to in-house manufacturers.

Issue 3: Performance Evaluations for Design Examinations

The potential benefit of conducting practical laboratory testing with Australian samples and under Australian conditions to confirm the manufacturer's intended purpose and claims appears largely redundant given the requirement for the manufacturer to provide data that is representative of performance in the Australian population.

Essential principle 15(1) states that "*An IVD medical device must be designed and manufactured in a way in which the analytical and clinical characteristics support the intended use, based on appropriate scientific and technical methods.*". An applicant must already provide data supporting compliance with this essential principle i.e. the applicant must demonstrate that an IVD's analytical and clinical characteristics are appropriate for its intended use in the Australian population.

The proposed *ad-hoc* performance evaluations for Class 4 IVDs encompass a much wider range of IVDs than the HIV and HCV IVDs which were previously subject to performance evaluations. The introduction of such evaluations would:

- Add a significant level of uncertainty into the timeline and requirements for approval. In some cases product will need to be supplied for the performance evaluation and the conformity assessment would take additional time, up to a year, to be completed.
- Add to the TGA's costs which would in turn need to be recovered from applicants in the form of higher fees. Conformity assessment fees for Class 4 IVDs in Australia are already very high compared to the size of Australia's IVD market.

It is considered that these factors would be a substantial disincentive for Class 4 IVDs to bring innovative products to Australia. The requirement for performance evaluations also has the potential to delay approval of latest healthcare technology by up to a year while the evaluation is performed.

However, if performance evaluations are considered necessary then explicit guidelines on which products would be subject to a performance evaluation need to be developed in consultation with industry. Such guidelines would be essential to provide industry with a degree of certainty regarding approval timelines and requirements.

It is noted that the current suggestions of the products that would be subject to performance evaluations e.g. products using a new technology, a new IVD used to detect a serious infectious disease, are skewed against innovative products. The criteria for conducting performance evaluations needs to be carefully considered so that the Australian population does not miss out on access to innovative diagnostic technologies.

Included in the scope of the guidelines must be the option for the manufacturer to conduct its own study(ies) to generate the evidence of the performance of the product with samples representative of the Australian population/or under Australian conditions. Such studies could potentially be quickly performed by the manufacturer, reducing the time to market, burden on the TGA and improving access to the latest healthcare offerings by the Australian population.

Issue 4: Regulation of tests for predisposition or susceptibility to disease

This proposal would provide an appropriate and clear pathway for the regulation of such tests.

The proposal to amend the definition of a medical device to the include predisposition and susceptibility tests is considered reasonable.

It is noted that the GHTF definition of an "IVD" includes products used for testing for predisposition so the proposal is consistent with harmonisation efforts in this regard. The final wording of the definition should align as closely as possible with the harmonised definition.