AusBiotech submission in response to the *Guidance for Class 4 in-house IVDs for screening Faecal Microbiota Transplant (FMT) donors*

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Introduction

AusBiotech welcomes the opportunity to submit a response to the TGA's draft *Guidance for Class 4 in-house IVDs for screening Faecal Microbiota Transplant (FMT) donors.*

AusBiotech is the Australian representative body for one of Australia's most innovative industries with a well-connected network of over 3,000 members in the life sciences industry, which includes biotherapeutics, medical technology (devices and diagnostics), food technology and agricultural biotechnology sectors.

The submission represents AusBiotech members actively engaged in delivering social and economic benefits to Australia through the commercialisation of biotechnologies and medical technologies, and in particular its members developing therapies in the emerging FMT industry.

AusBiotech welcomes the release of the guidance, however, there are components that are currently unworkable and unfeasible, and will jeopardize Australia's nascent but important FMT industry. It recommends:

1. Continuing the current Class 4 IVD exemption for the requirement for stool donor screening test kits permanently.
2. Further discussion between the TGA and industry to support and foster this emerging industry with a fit-for-purpose framework to screen FMT donors, given the small sample size, data validation and resourcing (cost, capacity and time) barriers being faced.

Guidance feedback

Support of regulation commensurate with risk

Australia's biomedical technology industry is supportive of the TGA's risk-based regulatory approach, where regulation is commensurate with the risks posed by the therapeutic good to best protect and advance public health.

IVDs are classified according to the health risk that may arise from an incorrect result. On behalf of industry, we contend that screening for enteric pathogens is beyond the classification rules of a '*high public health risk'*, as noted for Class 4 in-house IVDs. By increasing the classification level from 3 to 4, it will create additional and burdensome regulatory requirements for laboratories, who act as the manufacturer in the FMT process.

There is already a much higher quantity of stool donor screening tests required when compared to other biologicals, and the public health risk profile of each individual test that does not already have a Class 4 IVD, such as HIV or Hepatitis C, is significantly lower. Most of the laboratory tests for stool donor screening relate to detection of pathogens that, if transmitted, cause brief, self-limited or easily cured gastrointestinal infections. These enteric pathogens do not meet the standard for 'high public health risk' required for Class 4 IVD status that an incurable blood borne virus such as human immunodeficiency virus (HIV) does.

The IVDs are already ARTG-registered as a Class 3 or below, and by removing the Class 4 exemption in 2025, as proposed, will see additional regulatory requirements translate into real cost barriers, which in turn risks stifling Australian innovation in a newly emerging field with much global potential; importantly, implementing the proposed changes will not add additional improvements in product safety.

The entire range of blood and stool tests required to screen FMT donors is performed by a small pool of laboratories. If the testing provider has NATA accreditation, as suggested by the Guide's 'Pathways for compliance', and as such compliance to ISO 15189 and NPAAC requirements for in-house IVDs and a GMP licence, industry believes that this should be sufficient to maintain FMT tests as Class 3 or below in-house IVDs.

AusBiotech is concerned on the impact the proposed changes will have on the emerging biotech industry, without adding value to the existing quality and safety, and recommends continuing the current Class 4 IVD exemption for the requirement for stool donor screening test kits permanently.

Fostering innovation

As industry develops these life-enhancing therapies, it seeks to minimise potential infectious disease transmission events while simultaneously maximising FMT transplant access opportunities for all Australians.

All infectious disease screening recommendations, therefore, carefully consider turnaround times, test performance (for example, the risk of false positive or false negative results), and other logistical issues that may pose a risk to the donation process. These are considered alongside the benefits of screening for patient safety.

FMT already incorporates numerous screening tests for a wide range of microorganisms, with the current requirements for GMP for stool donor screening tests are already rigorous and resource intensive. The guidance proposes these tests be increased further despite, as noted above, not adding additional value to the existing quality and safety.

If the proposed guidance is implemented, then a significant number of mandatory assays are likely to fall under the requirement to shift from a class 3 or below to 4 IVD. Those in particular, where the analyte is a stool sample, will require significant investigation into an effective method to achieve this.

The ability to source appropriately qualified samples and the substantial time, effort, resources and cost to do is of concern to industry. As an emerging field, there is also potential for the range of FMT products to expand in the future, thereby placing additional and substantial current and future capability and capacity pressure on samples, resourcing and timing.

Whilst the Class 4 exemption is proposed until 2025, industry anticipates that the existing demand, in combination with the other resource needs, including financial burden, will make this difficult target date unrealistic. The additional and unachievable requirements, outlined below, will make the manufacture of FMT product in Australia unfeasible, and therefore the proposed changes are to the detriment of Australian patients.

It is expected that FMT donor test vendors are highly unlikely to register these tests as Class 4 IVDs, as proposed, given the currently limited commercial interest requiring them for a Class 2 Biological. This challenge has already been experienced by industry, with the discontinuation of some tests due to low volume demand, for example, the malaria confirmatory testing used for blood donors.

Industry is committed to ensuring a safe and effective supply of FMT in Australia, however, needs a framework that's fit-for-purpose in which to do so. AusBiotech recommends further conversation between industry and the TGA in order to overcome the barriers outlined, meet the outcome the TGA is seeking, and to foster Australia's emerging FMT sector.

Samples for validation

The guidance notes that "Contrived positive samples can be used to validate tests. Positive samples can also be prepared from a commercially acquired target analyte of known concentration and

spiked into a negative sample. For further consideration on how and when to use contrived samples please refer to NPAAC guidelines."

Validating the samples, as outlined in the guidance, is unfeasible. Generating sufficient data in such small sample sizes will be challenging and it is not possible to establish a known concentration for all different antibodies, as commercially-available products are not available for all analytes.

Limit of detection (LoD)

The guidance states, "As the population to be tested is asymptomatic donors, it is recommended to investigate the infective dose of the infectious agent in question so it can be compared to the LoD."

The infective dose is highly dependent on the susceptibility of that host to infection, which is highly variable and highly strain-dependent, for example, it would be impossible to do this for every serotype of Salmonella.

As there is no single infectious dose for all human hosts, there is no data available to determine this, particularly given the novel route of high-volume faecal inoculation via the lower intestine.

Many tests also have a lower limit of detection below the quoted infective dose, and there will be no way to increase the sensitivity of the test.

Sampling error is also likely to be an issue, given the intermittent excretion of many pathogens.

Conclusion

The standards outlined in the draft guidance do not add additional improvements in product safety, are too onerous and cost inhibitive for the limited providers in Australia, and places the ability to manufacture FMT as a Class 2 biological in in jeopardy.