Inspections Section
Manufacturing Quality Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Dear Sir/Madam,

Consultation: Good Clinical Practice Inspections Program

Medicines Australia welcomes the opportunity to provide comment on the Therapeutic Goods Administration (TGA) consultation on the Good Clinical Practice (GCP) Inspections Program.

Our submission has been prepared with the expert input of the joint sponsored Medicines Australia/Medical Technology Association of Australia/AusBiotech Research and Development Taskforce as well as Medicines Australia's Regulatory Affairs Working Group (RAWG). Members are selected for their significant experience and industry knowledge and bring a whole-of-industry perspective to the consideration of regulatory and research and development (R&D) issues that stand to impact the MedTech sector.

We would be happy to discuss or provide further comment on any aspect of our response and we appreciate being kept up to date on further developments.

Please feel free to contact Betsy Anderson-Smith if you would like further clarification on any aspect of our submission (banderson-smith@medaus.com.au).

Yours sincerely

Dr Vicki Gardiner
Director, Policy and Research
Medicines Australia

Medicines Australia broadly supports the implementation of a GCP pilot program if it is to provide assurance that GCP standards are being met in Australia, however there are a number of concerns regarding the proposed rational and approach outlined in this consultation.

Australia currently has a good reputation for conducting high quality clinical trials and Medicines Australia supports measures that will further "strengthen Australia as an attractive clinical research destination". However, Medicines Australia contends that whether the GCP inspection program will meet the stated objective of making Australia appear as a more globally attractive destination will greatly depend on the sampling strategy of the TGA program (compared to say FDA and EMA programs in particular) and how the program results are then communicated to global stakeholders. It would be more appropriate for the stated purpose of implementing this program to be to protect the rights, safety and wellbeing of subjects enrolled in clinical trials and to verify the integrity of the data collected. In addition, it should be considered how a TGA GCP inspection program would complement or harmonise with other international clinical trial regulators so that a consistent and complimentary approach for clinical trial oversight will result.

In implementing any GCP program, the TGA should:

- safeguard the current competitive environment,
- carefully consider how audit sites are chosen, and whether there are different objectives for different studies. For example: Industry sponsored versus non-industry sponsored trials,
- carefully consider whether a risk-based approach is applied and whether it would apply only for non-industry sponsored trials,
- articulate how the findings are envisaged to be used to improve the system.
- ensure the benefits that will accrue (ensuring rights, safety and wellbeing of Australian subjects enrolled in clinical trials and verify the integrity of the data collected) will be commensurate with the cost, time and effort required from investigators, study sites and sponsors in the conduct of such a program.

A TGA GCP Inspection Program will only be widely and rapidly effective in improving quality across Australia if the results of the program are then utilized in a systematic and health system wide manner:

Having a GCP inspection program locally may lead to improved standards, however this will only be achieved widely and rapidly if combined with a systematic approach in the health system to ensure that learnings from the inspection program are then disseminated widely and accompanied by other supporting actions (e.g. feeding into the National Clinical Trials Governance Framework currently being developed).

Ideally, an effective CT Consultative Forum/State Departments of Health would use the data and drive improvement programs targeted at identified deficiencies in a systematic manner.

Medicines Australia members have indicated that passive or limited diffusion of results will produce slow and limited improvements in site quality.

There are a number of concerns regarding the proposed rational and approach to using the data globally to make us appear more globally competitive The program is proposed to improve Australia's reputation for site quality and seems to imply global perceptions of site quality is currently an issue, however there is no data quoted to support this view. Medicines Australia would suggest that , if the TGA program uses a sampling strategy akin to the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA), the results will be expected to be little different to EMA and FDA findings in their home jurisdictions (given those programs already include Australian study sites as part of medicine pre-approval foreign study site inspections and the results from those inspections at Australian sites are similar to study sites in the home jurisdictions). Medicines Australia questions on

what basis would the expectation be otherwise as there is no systematic, health system wide, ongoing process improvement initiative in place in Australia that might produce a significantly better result.

By contrast, if the TGA program uses a targeting approach based on risk (e.g. more complex studies, more high-risk therapies, higher risk sites or sponsors, especially non-commercial sponsors), the results from the TGA program are likely to be worse than FDA or EMA programs as the TGA data set will be biased towards studies and sites with a different risk profile to the EMA and FDA programs (as these programs largely focus confirming the dependability and acceptability of data generated in study sites that support marketing applications). The results produced could therefore be counter-productive to the stated aim of improving global competitiveness and could even make Australia's GCP quality look worse than comparable countries (especially if a TGA inspection program is targeted at higher risk studies/sites). The use of such data externally would therefore need to be very carefully thought through and differences in program focus would need to be very effectively communicated or Australia's reputation may be inappropriately tarnished when such data is published.

The Consultation states that "Consultation with the UK Medical and Healthcare products Regulatory Agency (MHRA) has highlighted that a domestic GCP inspections program in the United Kingdom raised the standard of conduct and quality of clinical trials - particularly those sponsored by non-commercial organisations." However, there is no reference to the objective data that is being used by MHRA to support this assertion re impact on local trial quality. Such objective data would be useful to develop local metrics for the TGA program to measure any such local improvement in quality. Having such metrics, and developing these a priori, is currently not mentioned in this consultation. If the program is especially successful in raising the quality in studies sponsored by non-commercial organisations, this is unlikely to significantly improve Australia's perceived quality for global commercial sponsors as the sites used will often not overlap with non-commercial study sites.

Medicines Australia notes that improving risk in non-commercial trials is laudable but will not necessarily enhance Australia's global reputation for commercial trial conduct.

Further information is needed on how the findings of the audits are published or who they are sent to, to assess what impact this program will have on the Australian clinical trial environment.

Medicines Australia would like to make the following additional points regarding the consultation.

1. The proposal states that the proposed GCP inspections will 'address the potential risk of a decline in international recognition of Australian clinical trial data quality and integrity.' Further background or evidence as to why/if this may be a risk would be useful.

2. It is stated that 'a domestic GCP inspection program will address a gap in the current regulatory oversight of the conduct of Australian clinical trials' – Further detail should be articulated to demonstrate the size and nature of the perceived gap.

3. It is also stated that 'It will support the TGA's ability to identify and manage risk under the CTN and CTX schemes….' Medicines Australia understands that the current role of identifying and managing risk under the CTN scheme is delegated to HRECs, unless further information is requested under the Section 31A system.

4. Medicines Australia is concerned that the fees and charges outlined under the funding options where 'The cost of the TGA's regulatory services are recovered by the fees and charges levied on Australian Manufacturers and Sponsors' may increase, and questions why Australian companies should be hit for inspections that will be majority international Sponsor-focussed?

5. Medicines Australia seeks clarity on how this program will align with other current clinical trial initiatives, ensuring no duplication.

6. In the Clinical trial sponsorship section (in Appendix 1), IITs (non-commercial studies) are described as clinical trials conducted for public good. Medicines Australia is concerned that this may be perceived that industry-sponsored trials are not.

7. In Conduct of the pilot program section, clarity is needed on what constitutes a 'serious issue' and 'compliance powers'.

The rational that "A GCP inspections program will encourage compliance" appears flawed (at least for commercial sponsors) as global commercial sponsors are already subject to international HA inspections of their trial sites in Australia, e.g. FDA, EMA. There are already very large incentives for global commercial sponsors to work very hard at ensuring compliance as if a pre-approval inspection of an Australian study site resulted in the submitted study data being found to be unacceptable, the marketing authorisation for a new drug submitted to FDA or EMA may be delayed (or even rejected). Medicines Australia questions whether non-commercial sponsors would be encouraged to increase compliance if the results of the proposed TGA inspection do not carry some well-defined consequence such as impacting potential NHMRC funding etc.

The Consultation states that "It will support the TGA's ability to identify and manage risk under the CTN and CTX schemes and enhance the reputation of Australian clinical trials for quality and integrity". Medicines Australia contends that If the primary concern for the TGA is to manage risk under the CTN and CTX schemes (a valid reason for a TGA CGP inspection program) then that should be the core stated reason for the inspection program. To avoid assumptions being made, the TGA should state the risks they are concerned about, the basis and data to support this concern, and then design the program to confirm if this risk exists or not. It is critical to then ensure the data coming out of the program is used in a systematic way to feedback into improvement programs (e.g. early Phase accreditation or training programs), the communication on the nature of the program and the context for the results (especially to global stakeholders) is very well thought through and communicated.

Medicines Australia notes the National Clinical Trials Governance Framework currently being implemented aims to provide consistency through the implementation of standards for all sites undertaking clinical trials and has the potential to increase the quality and safety of studies. The TGA should consider the utility of this framework in ensuring the learnings from a TGA GCP inspection program are embedded into clinical trial study sites on an ongoing basis.

One of the stated benefits stated in the consultation paper is; "Local clinical sponsors and investigators will have greater confidence that their trials are conducted in a manner that meets international requirements…and the results of their trials are credible".

As previously discussed, Medicines Australia suggests this can only be achieved if there is an effective/extensive strategy to disseminate results (and education programs into the health system) that is also employed to ensure change across the clinical trials environment results in a lift to standards.

With regard to Sample Size, the Consultation states that "Although a number of Australian clinical trial investigative sites may have been inspected at some time in the past by an international regulatory agency, the great majority may not". Medicines Australia questions that even with a TGA inspection program introduced, will the % of local study sites inspected be appreciably increased?

Can the TGA estimate the number of study sites inspected by global HAs per annum in Australia now and what the expected % inspected under a TGA program? In addition, will this sample size be expected to produce adequate data to make decisions on GCP site conduct/quality in Australia that addresses whatever the stated objective of the program?

Medicines Australia is concerned that the proposal regarding fees is unclear; "GCP inspections conducted by comparable agencies are, with the exception of the MHRA, at no fee" - given the influence

of the MHRA on the design of this program, can we expect MHRA type tiered fees when the program moves out of pilot? Clarity on the statement "No fees will be applied to the pilot on ongoing GCP inspections programs, rather the costs will be absorbed by TGA's general charges revenue" is also required.

Additional comments referring to specific sections of the consultation include;

Section	Page	Comments
A Pilot GCP inspection program	5	**Scope** Further clarity around scope of this audit would be useful to clarify whether the pilot is focussing on site systems (i.e. looking at multiple studies/ sponsors conducted at a single site) or on a single site/ study. It appears the pilot is focused on inspections of investigator sites, and clear guidance is required as to whether this will be expanded to include sponsor inspections. **Site/ Study Selection** Clarity as to how the TGA intends to conduct a site or study risk assessment is required. Are there plans to utilise a risk assessment tool or clear criteria by which you will select audit sites? I.e. will there be parameters used to inform risk as seen in the PV inspections conducted by the TGA? They utilise a questionnaire to select sites to audit. **High-Risk Study Definition** The paper only provides an example of "early phase of new medicine or combination of medicines where there are safety concerns" as high-risk. Sponsor companies have an audit function and are subject to inspections by other HAs. We would suggest higher risk studies such as investigator initiated should also be included in this pilot to inform a future GCP Inspections program.
Conduct of the pilot program – Audit records	5	**Audit Records** • In the conduct of the study, the second bullet point refers to reviewing "*monitoring and auditing records*". Audit records are not filed on-site, and per ICH GCP (5.19.3), audit information should not be requested by the inspectors: "*To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings*." **Communication of Findings** • This document notes the following; "If an inspection of a clinical trial identifies serious issues with the conduct of the trial or data integrity then information of the observed issues would be released to the HREC and/or Authorising Institution." It should be confirmed if that refers to all findings, or only a subset (e.g. critical?). In some countries (e.g. MHRA) critical findings are escalated by the inspector to a next level (Inspection Action Group). Clarity is required as to whether there are any plans to escalate findings or create such a group.

		• The Inspection Report should be submitted to the investigator, who has the responsibility of the conduct of the trial. Sponsors would also want to be informed if the inspection is focused on 1 sponsor-study i.e. the sponsor would like to receive a copy of the report. • Clarity as to whether results will be made publicly available **Attendance at Opening/ Closing meetings** • Clarity of the inspectors' expectations for attendance at the opening/ close out meetings is required. We would expect the PI and site staff to be involved at a minimum.
Rationale for an Australian domestic GCP inspections program	6	Please provide references for the information supplied in this paper implying that this program will "address the potential risk of a decline in international recognition of Australian clinical trial data quality and integrity..." We do not agree with this perception and would like to understand the reason for this statement being included in this paper.
Benefits to those conducting clinical trials	7	To maintain Australia's competitiveness, the TGA should carefully consider the associated increased costs and delays if significant changes are made that might result from these GCP inspections. A\It should be noted that Australia is already an expensive market.
Funding options	8	Cost recovery must be commensurate with other TGA activities. Further detail on the TGA's proposed fee structure is required.
Additional Feedback	NA	Consider Workshare Proposal. To avoid duplication of work the TGA could collaborate with other regulatory agencies conducting inspections in this market.

In conclusion, the proposal to commence a TGA GCP inspection program in Australia has the potential to produce benefits for patients, investigators, institutions and sponsors in Australia, however, the current rational proposed (that such a program will improve Australia's global competitiveness) needs to be critically examined. It is entirely reasonable (and laudable) that such an inspection program be used by TGA to "identify and manage risk under the CTN and CTX schemes", however this should then become the central stated outcome and drive the design of the inspection program. This objective should be central to sample size, risk profiling, determining how identified risk is then effectively mitigated and prevented following the inspections.

Medicines Australia members have extensive experience with global Health Authority (HA) GCP inspection programs, the differences between the HA programs and the conduct of such inspections in practical terms (including within study sites in Australia). Medicines Australia members would be pleased to work closely with TGA on the design and implementation of any GCP inspection program to ensure the program will produce the desired outcomes in an efficient and practical manner.