

**From:** S  
**To:** Streamlined Submission: S  
**Cc:** S  
**Subject:** FW: Potential application - Ivermectin - Statistical principles for clinical trial design [SEC=OFFICIAL]  
**Date:** Friday, 21 May 2021 12:02:14 PM  
**Attachments:** [image001.png](#)  
[image002.png](#)  
[image003.png](#)

FYI

Kind regards: S22

S22

#### Strategic Lead – COVID-19 vaccine regulation

Medicines Regulation Division | Health Products Regulation Group  
 Australian Government Department of Health  
 T: S22 | M: 22 | E: S22 @health.gov.au  
 Location: TGA, 136 Narrabundah Lane Symonston  
 c/- PO Box 100, ACT 2606, Australia

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**From:** S22

**Sent:** Friday, 21 May 2021 12:01 PM

**To:** S47F @cdd.com.au>

**Cc:** S22 @health.gov.au>; S47F @gmail.com>; S22 @health.gov.au>

**Subject:** RE: Potential application - Ivermectin - Statistical principles for clinical trial design [SEC=OFFICIAL]

Good morning: S47F

Just reflecting on our conversation the other day, and I thought the following international guideline may be helpful. This guideline has been adopted by the TGA and describes the statistical consideration for clinical trial design, and indeed the sample size for a clinical trial. I'm mindful that the clinical trials that you describe to me (in brief) may not be sufficiently powered (ie your sample size may be too small) to enable conclusions to be drawn about the efficacy of your proposed treatment. If you haven't already done so, you may wish to consider having your clinical trial design reviewed by a biostatistician, as this biostatistics report is one of several key considerations for the TGA when evaluating your application.

Statistical guideline for clinical trials: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002928.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf)

Further, grateful if you can please confirm who will be the sponsor for this application.

Kind regards: S22

S22

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 T: S22 | M: 22 | E: S22 @health.gov.au  
 Location: TGA, 136 Narrabundah Lane Symonston  
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**From:** S47F @cdd.com.au>

**Sent:** Wednesday, 19 May 2021 7:37 PM

**To:** S22 @health.gov.au>

**Cc:** S22 @health.gov.au>; S47F @gmail.com>

**Subject:** RE: Potential application - Ivermectin - Australian sponsor [SEC=OFFICIAL]

Hi: S22

Thank you for speaking with me the other day.

I'm getting the data together and will send you information as per your points below about our Anti-Viral

Kind Regards,

S47F

Director, Centre for Digestive Diseases  
 Director, Microbiome Therapeutics Institute



S47F @cdd.com.au  
 PS22 | www.cdd.com.au  
 Level 1, 229 Great North Road, Five Dock NSW Australia 2046

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**From:** S22 @health.gov.au>

**Sent:** Monday, 17 May 2021 9:34 AM

**To:** S116 @benefel.com.au; S47F @cdd.com.au>

**Cc:** Streamlined Submission <streamlinedsubmission@health.gov.au>; S22 @health.gov.au>; S22 @health.gov.au>

**Subject:** RE: Potential application - Ivermectin - Australian sponsor [SEC=OFFICIAL]

Good morning: S116 and S47F

While the TGA can organise a meeting with your team, my understanding is that no meeting has been scheduled at this time.

There are a couple of elements that often help with the scheduling of a preliminary meeting and would be required from your team. I highlighted some of these elements in my previous email, such as having an Australian sponsor for the submission. In TGA experience, scheduling a preliminary meeting with your team as well as your Australian sponsor (<https://www.tga.gov.au/role-sponsor>) is very beneficial for your team to gain a full understanding of the application process and nuances as it relates to COVID-19 medicines. Similarly, providing the TGA with some preliminary information of your medicine and its clinical trial progress also help us help you, for instance:

- brief overview of the medicine
- clinical trial progress (proposed and conducted to-date)
- overseas regulatory status (authorisations, under evaluation)
- proposed manufacturing supply (if known)
- list of questions for the TGA (note that the TGA may provide written responses in lieu of a meeting) or meeting agenda

Please let me know if you need any information on sourcing a regulatory agent, or indeed whether it is your intent to be the Australian sponsor.

Kind regards: S22

S22

#### Strategic Lead – COVID-19 vaccine regulation

Medicines Regulation Division | Health Products Regulation Group  
Australian Government Department of Health  
T: S22 | E: S22 @health.gov.au  
Location: TGA, 136 Narrabundah Lane Symonston  
c/- PO Box 100, ACT 2606, Australia

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From: S11C @benefel.com.au <S11C@benefel.com.au>

Sent: Friday, 14 May 2021 3:08 PM

To: S22 @health.gov.au; S47F @cdd.com.au

Cc: Streamlined Submission <streamlinedsubmission@health.gov.au>

Subject: RE: Potential application - Ivermectin - The process begins - with Australia's safety in the face of Covid19 foremost on our minds - we race against the clock

**REMINDER:** Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Dear S22

Thank you for writing back to me.

While I remain in the loop, the key contact for this application will be S47F. He has informed me that a Zoom meeting has already been organized.

I do see the email below outlines a template path forward which I trust your office will work through with S47F in a collective approach to bring essential life-saving options for Covid19 to the Australian people in the fastest and safest way possible.

I am sure the TGA and John Skerritt recognise this is no ordinary application for some pain relief medication and this medication and its indications being applied for may (will) play a key role in opening up Australia and significantly reducing the hospitalisations and death tolls of the pending wave of Covid19 infections that Australians face.

Aside from this discussion S22, I can put you in direct touch with practicing world class Doctors in the US who are consistently reporting that 60% of the patients they are now treating for Covid19 symptoms are fully vaccinated; I say this so you will know that something more than Vaccines are needed in this fight against Covid19 and it is an urgent matter that Australia is prepared.

Every day saved in an efficient joint path through this process is critical in reducing the resultant hospitalization and death, as will be demonstrated in with the data that will be presented. It need to be stated that the timing for this application is targeted to be within 2 weeks; delays beyond this will likely result in casualties that would have been avoided but for the length of the time of this application process.

S47F brings with him a team that should streamline this process, nevertheless, any assistance and guidance you can afford in your senior position in this process will play a critical role in the outcome for all Australians.

Again, thank you for writing and responding so quickly.

Best Regards

S 11C(1)(a)

S22

From: S22 @health.gov.au

Sent: Friday, 14 May 2021 1:14 PM

To: S11C @benefel.com.au; S47F @cdd.com.au

Cc: Streamlined Submission

Subject: Potential application - Ivermectin - further information [SEC=OFFICIAL]

Dear Mr S11C(1)(a),

Thank you for contacting the TGA regarding your potential application for ivermectin. As the Strategic Lead for COVID-19 Vaccine Regulation, I head the TGA's COVID-19 medicines regulation coordination activities.

Applications for COVID-19 medicines are being treated with the greatest priority as part of the TGA's response to the COVID-19 global pandemic. The TGA is considering applications for COVID-19 medicines under the Prescription medicine provisional approval pathway (conditional approval) and/or the standard (full) registration pathway, based on the clinical trial data for individual applications.

#### Sponsor

Please note that an Australian sponsor is required for submission of an application to the TGA. The sponsor has certain legal obligations for the product under the [Therapeutic Goods Act 1989](#) and associated legislation. You may find it helpful to consider using a regulatory affairs consultant who is familiar with TGA processes, when you are preparing your submission dossier. The TGA is unable to provide recommendations for regulatory affairs consultants or sponsors, but in the first instance you may like to reach out to an [regulatory affairs consultant](#) via the appropriate industry associations for additional advice and assistance with Australian regulatory requirements. Sponsors are encouraged to seek independent legal advice to ensure that all legislative requirements are met.

#### Regulatory framework

The TGA website provides detailed guidance on the regulatory framework and on submitting an application to the TGA, including data requirements and fees. Please see the following:

- [Australian Regulatory Guidelines for Prescription Medicines](#) (ARGPM) includes:
  - general guidance
  - specific guidance on technical requirements
  - format of the Common Technical Document (CTD) dossier
  - data requirements across Modules 1-5 of the CTD dossier (i.e. Australian-specific information, quality, safety, efficacy)
- [International scientific guidelines](#) adopted in Australia. The TGA closely aligns its regulatory approaches to therapeutic products with those of comparable international regulatory counterparts wherever possible. In general terms, the TGA has similar expectations for submission dossiers and their evaluation, including following international scientific guidelines, however there are often national-specific requirements that a sponsor will also need to give consideration to.
- [Provisional approval pathway](#) - The sponsor must first apply for provisional approval determination based on the relevant [eligibility criteria](#); if the criteria are met and the product is granted provisional determination, then an application can be made for provisional registration. Phase 1/2 Clinical trial data (Module 5) are usually insufficient to obtain a positive provisional determination outcome; in general, promising early Phase 3 data on safety and efficacy is required. Quality (Module 3) and nonclinical (Module 4) data should be of sufficient maturity before submitting an application for provisional registration. Sponsors should have defined clinical and manufacturing development plans for their COVID-19 medicine, and be able to provide details to the TGA. Sponsors should identify proposed supply chains and ensure GMP clearance applications for manufacturing sites are submitted to the TGA as early as possible.
- [Fees and charges](#) for prescription medicines - The relevant fees will depend on the proposed application type and proposed pathway for your product.

#### Pre-submission meetings

The TGA strongly recommends that sponsors hold a pre-submission meeting with the TGA prior to submitting an application for a COVID-19 medicine. The TGA can arrange meetings to discuss, in broad terms, the TGA's **regulatory framework and administrative processes** supporting COVID-19 medicine applications. Please contact [streamlinedsubmission@health.gov.au](mailto:streamlinedsubmission@health.gov.au) with 'COVID-19 medicine' in the subject line, and state that you are seeking a general meeting with the TGA. A **formal technical pre-submission meeting** with TGA evaluators can be requested when there is a clear clinical development plan, and preferably once Phase 2/3 studies have been fully enrolled and initiated, and that there is a clear ability to transition from provisional registration to full registration

Please review the [pre-submission meeting guidance](#) and [meeting request form](#). The TGA would be happy to arrange a pre-submission meeting once you have submitted your meeting request, including a technical briefing package that provides details on your proposed product:

- brief overview of the medicine
- clinical trial progress (proposed and conducted to-date)
- overseas regulatory status (authorisations, under evaluation)
- proposed manufacturing supply (if known)
- list of questions for the TGA (note that the TGA may provide written responses in lieu of a meeting)

I trust the above information addresses your queries.

Kind regards: s22

s22

#### Strategic Lead – COVID-19 vaccine regulation

Medicines Regulation Division | Health Products Regulation Group  
 Australian Government Department of Health  
 T: s22 | ES22 @health.gov.au  
 Location: TGA, 136 Narrabundah Lane Symonston  
 c/- PO Box 100, ACT 2606, Australia

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**From:** [PEGG, Grant](#)  
**To:** [s47F @bigpond.net.au](#); [s47F @cdd.com.au](#)  
**Cc:** [s47F @cdd.com.au](#); [s 11C\(1\)\(a\) \\_gmail.com](#); [s47F @gmail.com](#); [SKERRITT, John](#)  
**Subject:** Follow-up from 30 August meeting [SEC=OFFICIAL]  
**Date:** Friday, 10 September 2021 1:39:00 PM  
**Attachments:** [Relevant guidance for consideration.docx](#)  
[Comments on the clinical study synopsis.docx](#)  
[Considerations when applying to register medicines.docx](#)  
[image001.png](#)

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Dear [s47F](#) and [s47F](#),

Thank you for attending the videoconference on 30 August 2021 providing us with an update on the status of ivermectin triple therapy. At the meeting, we advised that we would provide you with some additional information and feedback.

Please find three documents attached which include:

- **Considerations when applying to register medicine/s for a new indication** – general points to consider across the various evaluation domains when preparing to make an application to the TGA
- **Relevant guidance for consideration** – links to regulatory guidance and information about Literature Based Submissions
- **Comments on the clinical study synopsis** – feedback on the draft study synopsis

We hope this information is useful.

Kind regards,

Grant

**Dr Grant Pegg**

Assistant Secretary

---

Medicines Regulation Division | Health Products Regulation Group  
 Prescription Medicines Authorisation Branch  
 Australian Government Department of Health  
 T: [s22](#) | E: [grant.pegg@health.gov.au](mailto:grant.pegg@health.gov.au)  
 Location: Therapeutic Goods Administration GD 63  
 PO Box 100, Woden ACT 2606, Australia

**Click [here](#) for the latest information on COVID-19**

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## Comments on the clinical study synopsis (draft 13.8.2021)

In the context that the proposed study may be used for a future regulatory application, the following preliminary comments are provided for the sponsor's consideration. Please note that these comments are not exhaustive or binding, nor should they be interpreted to pre-empt or replace the TGA's evaluation process that would be undertaken following receipt of an application. Sponsors are strongly encouraged to seek their own advice to ensure that regulatory requirements are met.

### General comments

- The phase of the study should be clarified.
- For regulatory purposes, dose selection and proposed regimen would need to be justified.
- The power of the study should be carefully considered.
- The COVID-19 evidence taskforce definition of mild and moderate disease for inclusion in the study should be clarified. The taskforce recommends that patients with moderate disease (SpO2 >92% with up to 4L of O2) should be managed in hospital, when possible.
- Confirm that continuous telemonitoring is proposed (i.e. not intermittent).
- The study question should be clarified. Is it to evaluate the proportion of subjects who will achieve the endpoint following randomisation or the days required for subjects to achieve the endpoint following randomisation?

### Comments on the primary endpoint

- The clinical justification/correlation of the primary endpoint (as a clinical test rather than outcome measure) should be carefully considered, in particular:
  - how the oxygen saturation level measured by telemetry/oximetry is closely correlated with clinical recovery
  - how subjects, for example with chronic lung diseases who may recover from COVID-19, but not be able to achieve oxygen saturation >98% will be managed
  - how this endpoint would translate to a potential indication for the medicines.
- The timepoint for the assessment of the primary endpoint should be made clear.
- Measurement precision should be carefully considered/controlled/validated given the choice of endpoint and the self-test proposal. How will user error be managed?
- In accordance with relevant guidance, the choice of clinically meaningful measures to assess effectiveness should be strongly considered.

**Comments on the inclusion criteria**

- The requirement of SpO2 < 95% could potentially exclude some mild symptomatic COVID-19 patients who may have normal SpO2 levels.
- Will the study stratify or focus on COVID-19 patients who are at high risk of developing severe COVID-19?
- Will the study include COVID-19 patients who are at an early stage of symptom onset (e.g. within 5-7 days of symptom onset) or COVID-19 patients with any duration after symptom onset?
- Will the study include people with any vaccination status (vaccinated and unvaccinated)?
- Will the study exclude patients who are concomitantly receiving another COVID-19 treatment/symptom management?

## Considerations when applying to register medicine/s for a new indication

Below is a non-exhaustive list of items that should be considered by the sponsor prior to making a registration application.

### General

#### Product sponsorship

The Australian sponsor is the legal entity responsible for the medicine/s in Australia. The sponsor is responsible for making the application for registration of the goods and also has legislated post-market responsibilities. Further details are available at: <https://www.tga.gov.au/role-sponsor>

#### Pharmacovigilance

Sponsors of registered goods also have pharmacovigilance responsibilities, these are outlined at: <https://www.tga.gov.au/publication/pharmacovigilance-responsibilities-medicine-sponsors>

#### Advisory Committee on Medicines

For an extension of indications application, subject to Delegate considerations, it is likely that advice would be sought from the independent clinical expert Advisory Committee on Medicines (ACM). The Delegate may seek advice from the ACM on a number of matters, including but not limited to clinical issues. ACM advice is considered by the Delegate when making a decision to register a product.

#### Dossier format

The dossier submitted must conform with the Common Technical Document format: <https://www.tga.gov.au/publication/common-technical-document-ctd>

From 1 November 2021, the Therapeutic Goods Administration (TGA) will begin a staged transition to Electronic Common Technical Document-only (eCTD-only) for all prescription medicines:

<https://www.tga.gov.au/electronic-submissions>

### Quality and Manufacturing

- If domestic manufacturing sites are being used, these will need TGA licences. If a new manufacturing site is being proposed, obtaining a new licence may take some time.
- If overseas manufacturing sites are being used, the sponsor will need to demonstrate appropriate GMP. This can be achieved in multiple ways, depending on existing overseas regulatory requirements applicable to those sites (mutual recognition agreements with comparable regulators etc) but in some instances a TGA inspection may be required.
- Manufacturing quality would need to be assured within the application dossier, including batch release/QA specifications (where relevant).
- Further information about manufacturing requirements is available at: <https://www.tga.gov.au/manufacturing-therapeutic-goods>

## Clinical

- Is the product's dose form and strength the same as a currently approved product?
- Are there data linking the proposed product with the currently registered product? This may include bioequivalence data depending on the nature of the application.
- Is it a single ingredient, composite pack or fixed dose combination?
- How does each component contribute to the product's efficacy and/or safety?
- Are there data on interaction between the components?
- What is the proposed dosage regimen and duration of treatment and is this supported by clinical trials?
- Have there been dose ranging studies to investigate different doses to select the optimal dose?
- Are there any drug interaction studies with other treatments?
- Are there well-designed and powered studies to determine efficacy, eg RCTs using the same products in the same combination and dose?
- Are there any non-supportive studies?
- Are there any ongoing studies and when are they expected to be completed?
- Who is the target population for treatment and what stage of disease is proposed for treatment?

## Toxicology (non-clinical)

- Are there any appropriate animal models of COVID-19 infection to test the proposed treatment's efficacy?
- Are there toxicology data supporting the dose proposed for humans?
- Are there any *in vitro* or *in vivo* animal studies that could explain the proposed therapeutic product's mechanism of action?
- Are there any pharmacokinetic/toxicokinetic data from animal studies supporting the safety and pharmacology/efficacy studies?
- Are there any *in vitro* or *in vivo* studies that have looked at the potential pharmacological, pharmacokinetic and toxicological interactions with the ingredients in the proposed therapeutic product and with other drugs that patients may take?
- Have you completed any studies in animals that have investigated the effects on fertility, reproduction and development?
- Have you completed any toxicity studies in juvenile animals?
- Were safety-related studies conducted under GLP conditions? Do you have information on the active ingredients' batch numbers and do you know their impurity profiles?

## Risk Management Plan

- It is likely that a Risk Management Plan (RMP) would be required, as is it is for other COVID-19 treatments. RMP requirements are detailed at: [www.tga.gov.au/publication/risk-management-plans-medicines-and-biologicals](http://www.tga.gov.au/publication/risk-management-plans-medicines-and-biologicals)

## Guidance for Literature Based Submissions

- The TGA website includes information on literature based submissions (LBS) that covers pre-submission guidance, dossier requirements and systematic literature searches:  
<https://www.tga.gov.au/publication/literature-based-submissions>
- The requirements for each module are discussed on the TGA website. Please note that literature-based data sets are not suitable for the quality (Module 3) component of an application as published reports rarely include sufficient validation information. A conventional Module 3 dossier should be submitted for all applications with a quality component.
- Prior to lodging the Pre-submission Planning Form (PPF) for a LBS, the TGA will need to have reviewed and provided written agreement for the literature search strategy, including the databases to be searched, and the criteria for determining which search results are to be included/excluded in the application dossier.
- In situations where the methodology or regulatory approach needs further consideration/discussion, a pre-submission technical meeting is strongly encouraged. Questions about pre-submission issues can be directed to:  
[streamlinedsubmission@health.gov.au](mailto:streamlinedsubmission@health.gov.au)

## Relevant clinical guidance for consideration

Based on preliminary information presented by the sponsor, the following guidance is likely to be relevant to the application wholly, or in part:

- **Points to consider on application with 1. meta-analyses; 2. one pivotal study**  
([https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-application-1meta-analyses-2one-pivotal-study\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-application-1meta-analyses-2one-pivotal-study_en.pdf))

In particular, section III.2 states:

*In cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, and in the regulatory evaluation special attention will be paid to:*

- *The internal validity. There should be no indications of a potential bias.*
- *The external validity. The study population should be suitable for extrapolation to the population to be treated.*
- *Clinical relevance. The estimated size of treatment benefit must be large enough to be clinically valuable.*
- *The degree of statistical significance. Statistical evidence considerably stronger than  $p < 0.05$  is usually required, accompanied by precise estimates of treatment effects, i.e. narrow confidence intervals. The required degree of significance will depend on factors such as the therapeutic indication, the primary endpoint, the amount of supportive data and whether the alternative analyses demonstrating consistency are pre-specified. When the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the lower 95% confidence bound is well away from the non-inferiority margin.*
- *Data quality.*

- Internal consistency. Similar effects demonstrated in different pre-specified sub-populations. All-important endpoints showing similar findings.
- Centre effects. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect.
- The plausibility of the hypothesis tested

- **Guideline on clinical development of fixed combination medicinal products** (<https://www.tga.gov.au/sites/default/files/ewp024095enfin.pdf>)

In particular, section 6 states:

*As a general rule, the choice of each substance in the fixed combination as well as the whole concept on which the rationale for the fixed combination is based have to be fully justified; this can be achieved by taking into account mode(s) of action, pharmacokinetics, and treatment recommendations for a given clinical setting.*

- **COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry** (<https://www.fda.gov/media/137926/download>)

In particular, part III.A.2 states:

*FDA strongly recommends that drugs to treat COVID-19 be evaluated in randomized, placebo-controlled, double-blind clinical trials using a superiority design. In some situations, use of an active control with a superiority or noninferiority design may be appropriate.*

*and part III.A.3 states:*

*The drug development program should evaluate the effect of the investigational drug relative to placebo or an active comparator on clinically meaningful aspects of the disease. The relevance and appropriateness of measures may depend on the mechanism of action of the drug, the population studied, the clinical setting, the phase of drug development, and/or baseline disease severity (see Appendix A).*

- It is also recommended that the sponsor review the various other adopted guidelines for prescription medicine applications which may be relevant to the application at: <https://www.tga.gov.au/ws-sg-index>