Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22

RE: TGA Pharmacovigilance Reinspection of s22

Please find attached the inspection report for the remote pharmacovigilance inspection of s22 conducted by the Therapeutic Goods Administration on s22 2023.

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021)
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as **APPENDIX I**).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Commitment Tracker.

For certain deficiencies, you may be requested to submit objective evidence of corrective or preventive actions after their completion dates. Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22 2023

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor Address:	s22
Main site contact:	s22 Qualified person responsible for pharmacovigilance in Australia
Inspection Type:	Reinspection
Method of Inspection:	Remote
Inspection Scope:	• To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines • To verify sponsor actions to address previous inspection findings
Inspection date/s:	s22 2023
Inspector/s:	s22 (Lead inspector), s22 (co-inspector) and s22 (co-inspector)
Inspection Finding Summary:	0 Critical Deficiencies 1 Major Deficiency s22
Date Report issued to Sponsor:	s22
Reference:	E22-633631

Contents

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Introduction

s22 The purpose of the reinspection was to evaluate changes to the sponsor PV system, including the corrective and preventive actions taken, to address the inspection deficiencies identified in the initial inspection. The inspection also evaluated sponsor ongoing compliance with applicable Australian PV regulations and guidelines.

In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021) (*Pharmacovigilance Guidelines*)
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

All acronyms used in this report are listed in **APPENDIX III**

Company background

s22 is the subsidiary of parent company, s22 based in s22 was established in s22 and it is the sponsor of s22 products registered on the Australian Register of Therapeutic Goods (ARTG). At the time of the inspection, s22 sponsor products were supplied in Australia: s22 both distributed by s22 , and s22 , distributed by s22

s22 appointed a third party service provider s22 based in Australia to provide PV services including the role of the Australian pharmacovigilance contact person (A-PVCP) and Qualified Person Responsible for Pharmacovigilance in Australia (QPPVA).

No post-registration studies or programs involving the products have been initiated by the sponsor thus far.

The s22 team was involved in multiple pharmacovigilance activities, including case processing, literature searches, significant safety issues management, signal detection, management of the reference safety information and quality management system.

Brief report of the inspection activities undertaken

Scope of reinspection

The reinspection was conducted remotely via videoconference and included a review of both local and global PV systems. Company personnel from s22 attended the inspection via videoconference.

The reinspection was conducted through interviews and review of documents (including searches of PV, medical information (MI) and product quality complaint (PQC) databases). The PV topic areas reviewed during the inspection focussed on the systems and processes which were associated with the deficiencies identified during the previous inspection and included a review of:

- The collection, processing and reporting of spontaneous adverse reaction (AR) reports
- The management of significant safety issues (SSIs)

- The management of reference safety information (RSI)
- The quality management system (QMS)
- The role of the A-PVCP and QPPVA
- Contracts and agreements relevant to the PV system

Documents submitted prior to the reinspection

Inspectors referred to the Corrective Action and Preventative Action (CAPA) Plan associated with the initial inspection of the sponsor s22 Other specific documents including for example, PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the company prior to the inspection.

Conduct of the inspection

In general, the inspection was conducted in accordance with the Inspection Plan (attached as **APPENDIX II**).

Tabulated summary of inspection deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing and reporting ARs and special situation reports received from spontaneous sources, were reviewed during the reinspection. This included a review of all Australian reports received by the company during s22 When required, the narrative and source documentation for specific cases were analysed. Deficiencies related to the s22 of ARs are described in s22 Major Deficiency 1 respectively.
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of company products were not reviewed during the reinspection.
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the reinspection. s22
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the reinspection. s22
PAC	The procedures for managing PV PAC, including submission of Periodic Safety Updates Reports (PSURs), maintenance of Risk Management Plan (RMP) documents and implementing RMP commitments, were not reviewed during the reinspection.

Role of the A-PVCP and QPPVA	During the reinspection, the roles and responsibilities of the A-PVCP and QPPVA were reviewed. s22
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and standard operating procedures (SOPs), was reviewed during the reinspection. s22

List of deficiencies identified during the inspection

Critical deficiencies

Nil Critical deficiencies were identified during the inspection.

Major deficiencies

1. Deficiencies in reporting serious adverse reactions (SARs) to the TGA

1.1. Failure to submit SAR reports from the literature

In accordance with the *Pharmacovigilance Guidelines*, you **MUST** report all serious adverse reaction cases occurring in Australia that are identified through screening the worldwide literature as soon as possible and no later than 15 calendar days from receipt.

If you believe that there is a real patient involved (without any identifiers), it is considered sufficient for reporting.

a) Example 1

A review of sponsor management of the literature article, "s22 revealed one SAR report that should have been recorded in the sponsor safety database and reported to the TGA by s22. Details of the case are provided in the table below:

Day 0	Product	Verbatim description	Serious?	Patient	Due date to the TGA	Delay to the TGA
s22			Y (hospitalisation)	One patient	s22	210 days at the time of Inspection Day 3.

Upon receipt of this article, the sponsor recorded one cluster case s22 which referred to a group of patients. The sponsor informed that the case was not submitted to TGA since there were no individual patient identifiers. No report had been notified to the TGA at the time of the inspection.

b) Example 2

A review of sponsor management of the literature article, "s22 ", revealed one SAR report that should have been recorded in the sponsor safety database and notified within 15 days of Day 0 to the TGA. Details of the case are provided in the table below:

Date of Embase alert	Citation	Product name	Case report details identified by inspector	Sponsor comment during inspection
s22				No case was created for the below article as company suspect was not reported in the abstract.

Further details of management of this publication are discussed in s22

1.2. Late submission of a SAR report

In accordance with the *Pharmacovigilance Guidelines*, all serious Australian adverse reactions **MUST** be reported to the TGA within 15 days of receipt by the sponsor.

Out of a total of two initial SAR reports submitted to the TGA by the sponsor in s22 one report s22 was submitted late to the TGA with a delay of 20 days. Further details are summarised in the table below:

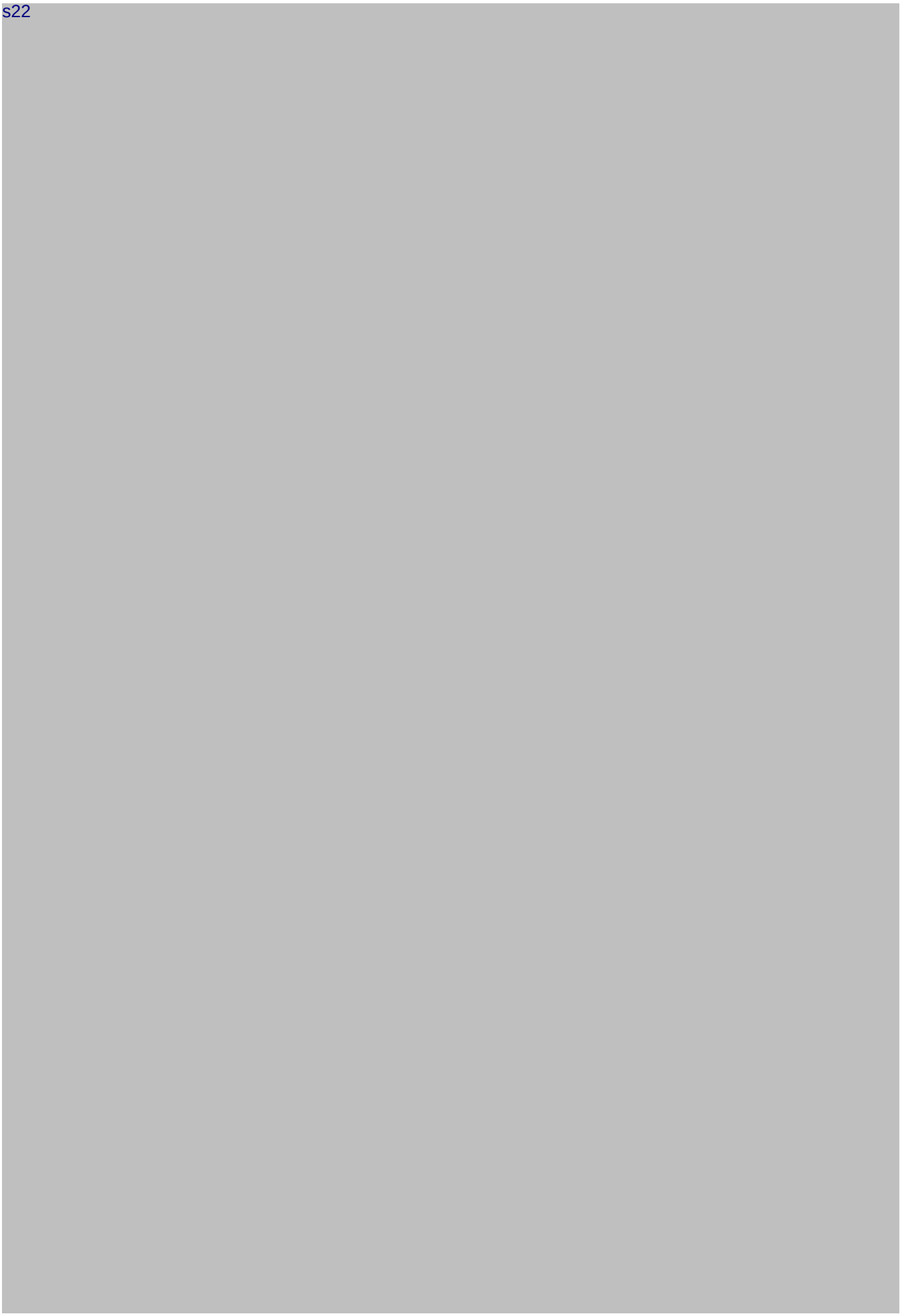
Initial receipt date by distribution partner (s22)	Date of case transfer to sponsor	Due date to the TGA	Date of submission to the TGA	Delay to the TGA
s22				20 days

According to the s22 were responsible to forward AE and special situation reports to the sponsor within s47G(1)(a) and s47G(1)(a) following receipt by any personnel or contractors of s22 The exchange of case s22 therefore represented a deviation to the Pharmacovigilance Agreement (PVA). A Root Cause Analysis (RCA) and CAPA Plan was initiated by the s47G(1)(a) PV service provider in response to this deviation on s22 and was closed on s22 .

s22 was received to the sponsor 20 days after Day 0. Whilst it was not possible for the sponsor to achieve an on-time submission of this report to the TGA due to the delay from s22 , it was noted that following receipt by the sponsor, the report was not notified to the TGA until the s22 s22 , 15 days after sponsor receipt of the case. The portion of the overall delay originating from the case processing time by the sponsor was not addressed in any CAPA.

Inspectors acknowledge that the sponsor informed that they will henceforth prioritize such cases received late from any source to reduce the length of the submission delay to the TGA.

s22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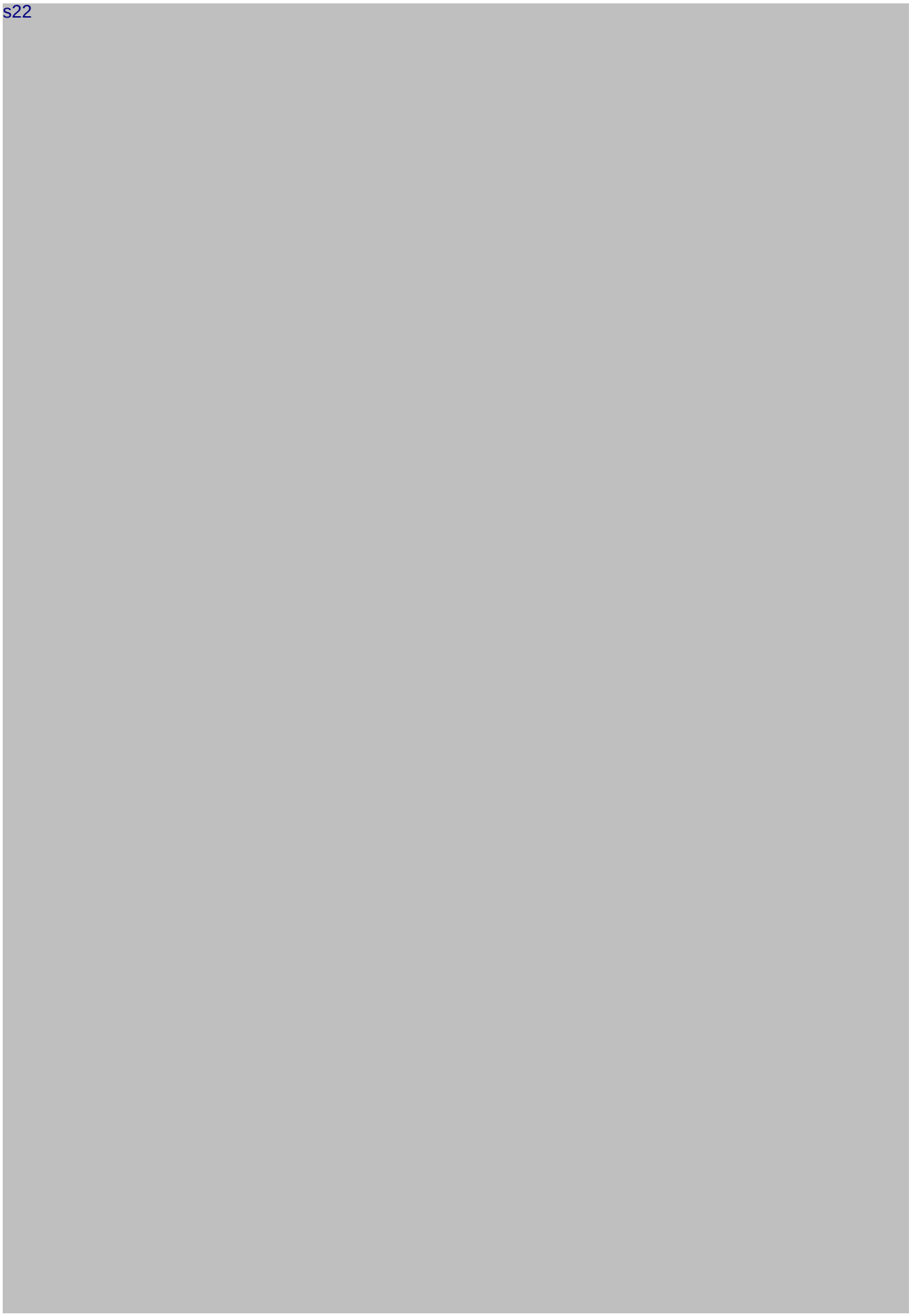

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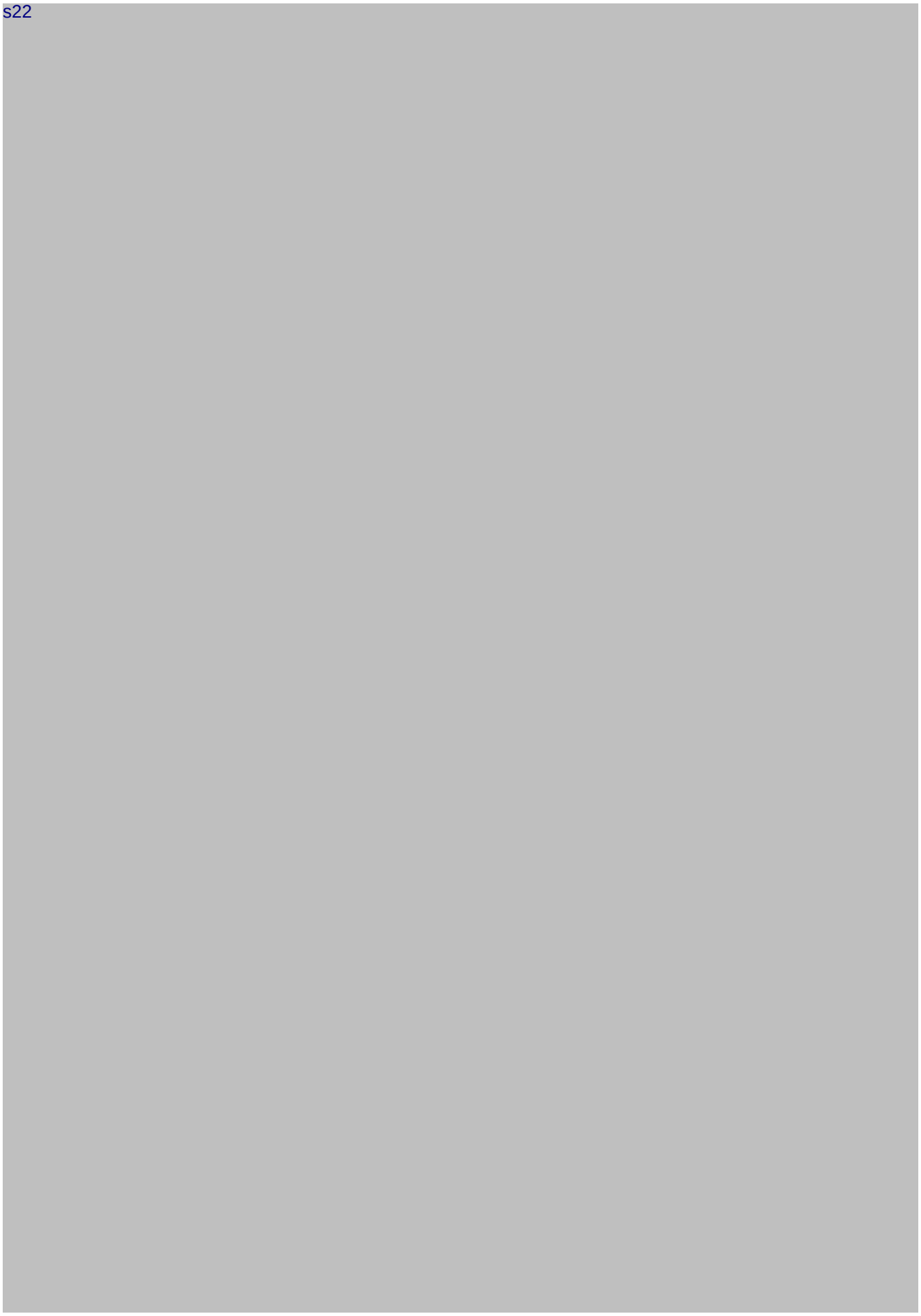

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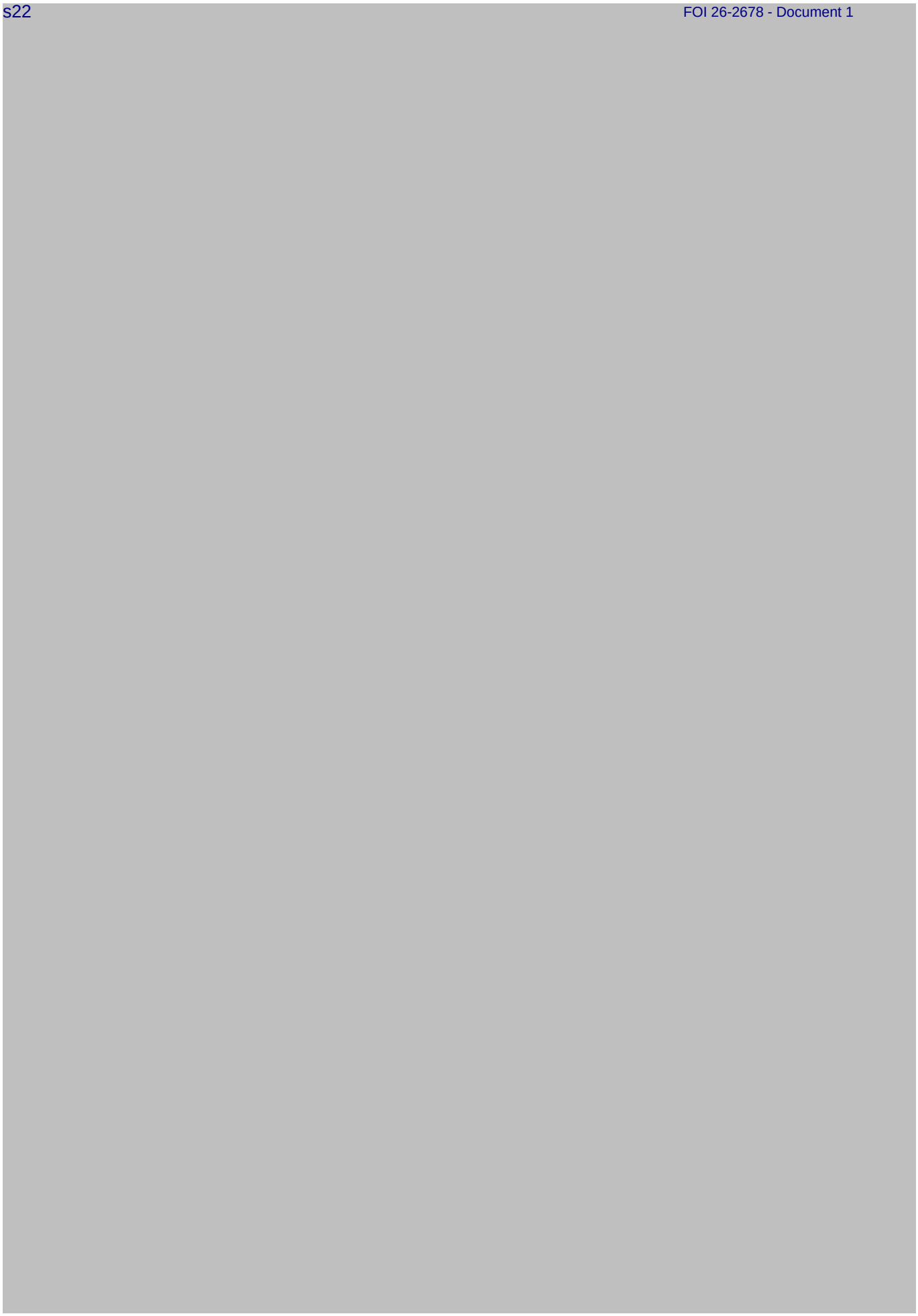

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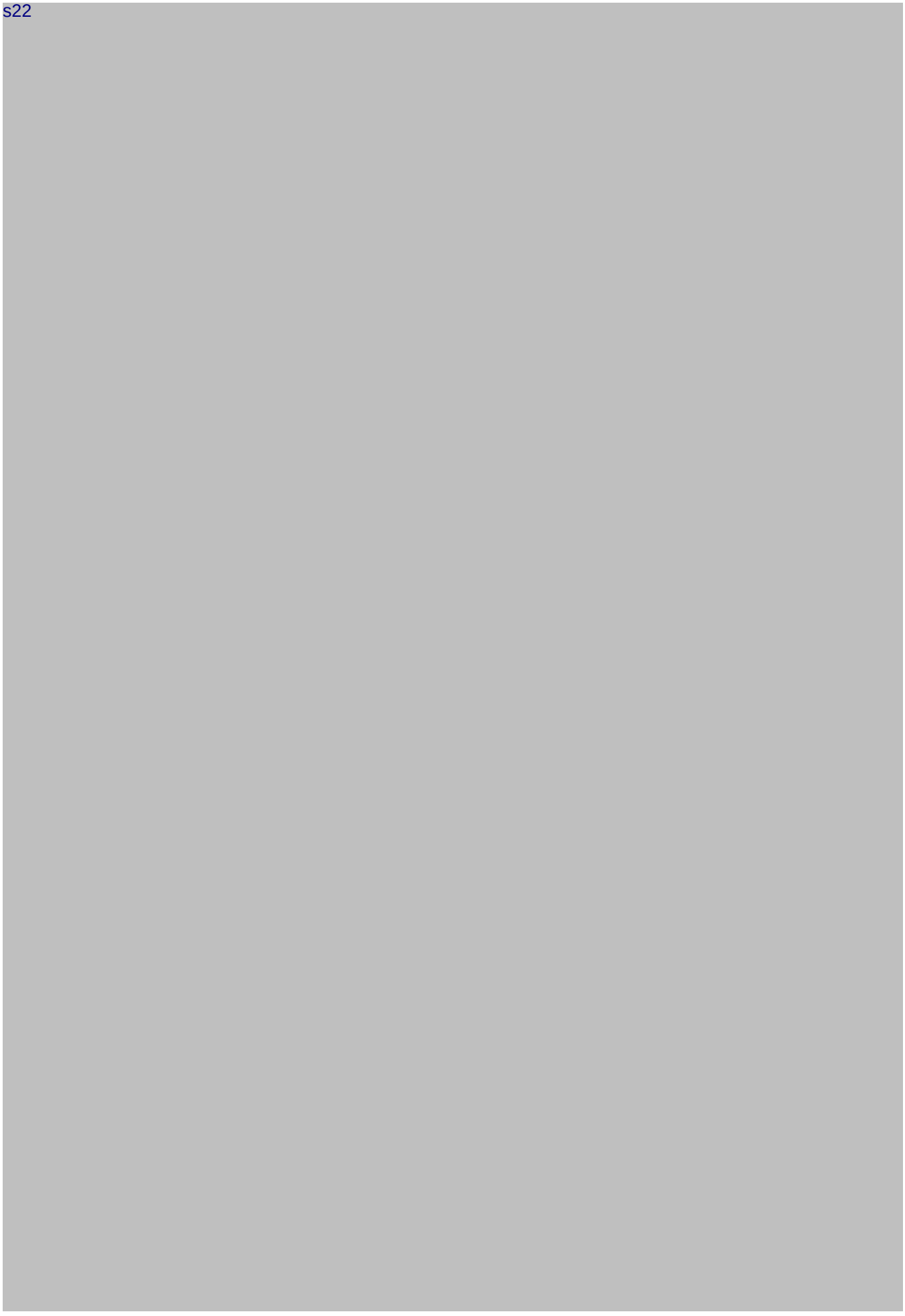
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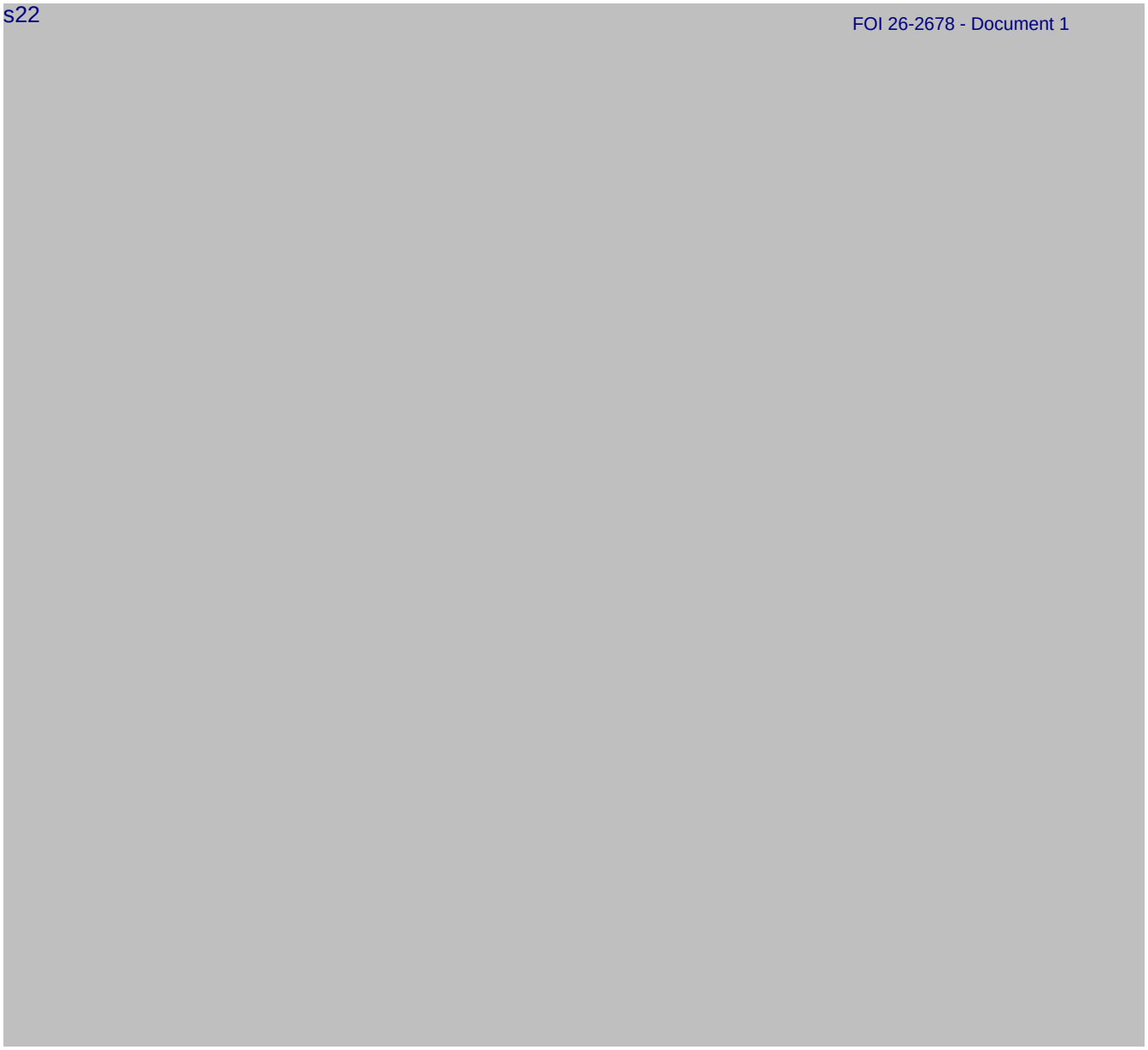


APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Pharmacovigilance Inspection Plan

Sponsor name:	s22
Sponsor address:	s22
Inspection type:	Reinspection systems-based (Remote)
Inspection dates:	s22 2023
Inspectors:	s22 (lead inspector), s22 (co-inspector), s22 (co-inspector)

Time (AEDT)	Activity	Staff involved
	PRE-INSPECTION CALL s22	
1:00pm	**Pre-inspection meeting** • Inspection logistics • Testing audio, video, screen sharing • Q&A	**TGA** s22 **Sponsor Staff** s22
	DAY 1 s22	
11:30am	**Opening meeting** • Introductions • Attendance • Scope • Confirmation of Inspection Plan	**TGA** s22 **Sponsor Staff** s22
	Company Presentation Overview of the implementation of the CAPA plan from the last TGA Pharmacovigilance Inspection (30 mins)	
1:00pm	**LUNCH**	
2:00pm	**Review of Agreements** • Safety Data Exchange Agreements (SDEA)	**TGA** s22

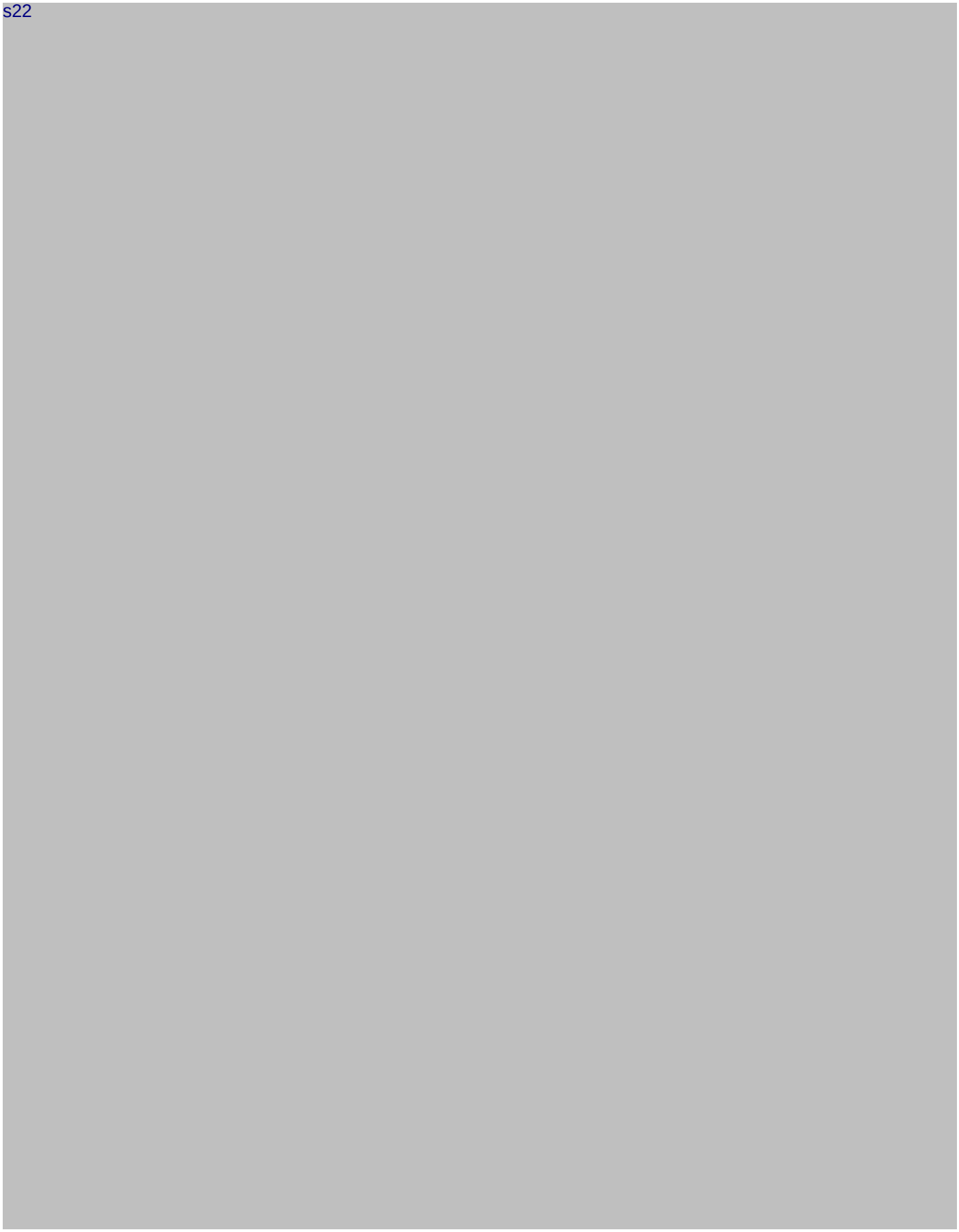
	• PV agreements	s22 **Sponsor Staff** s22
	DAY 2 s22	
2:00pm	**Role and responsibilities of the A-PVCP and QPPVA:** • Oversight • Training • Interaction with business partners and global headquarters	**TGA** s22 **Sponsor Staff** s22
	DAY 3 s22	
10:00am	**Cut-off for document delivery for the closing meeting**	
3:30pm	**Closing meeting**	**TGA** s22 **Sponsor Staff** s22

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
AEDT	Australian Eastern Daylight-Saving Time
s22	
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
CAPA	Corrective and Preventative Action
CIOMS	Council for International Organizations of Medical Sciences
CMI	Consumer Medicine Information
MI	Medical Information
MR	Medical Reviewer
PAC	Post-approval commitments
PI	Product Information
PQC	Product Quality Complaint
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreement
PVIP	Pharmacovigilance Inspection Program
QMS	Quality Management System
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
RMP	Risk Management Plan
RCA	Root Cause Analysis
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
TGA	Therapeutic Goods Administration

s22



Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22

RE: TGA Pharmacovigilance Inspection of s22

Please find attached the inspection report for the remote pharmacovigilance inspection of s22 conducted by the Therapeutic Goods Administration (TGA) on s22 2023.

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*. The purpose of the inspection was to assess compliance with the relevant pharmacovigilance legislation and guidelines and the conditions specified in the relevant approvals for registration or listing on the Australian Register of Therapeutic Goods (ARTG), and any subsequent variations.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021)
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as **Appendix I**).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Commitment Tracker.

For certain deficiencies, you may be requested to submit objective evidence of corrective or preventive actions after their completion dates.

Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed. In some circumstances, a re-inspection may be required to ensure completion of such activities.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Senior Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor address:	s22
Main site contact:	Pharmacovigilance Manager and Australian Pharmacovigilance Contact Person
Inspection type:	Routine, system-related inspection
Method of inspection:	Remote
Inspection scope:	To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines
Inspection date/s:	s22 2023
Inspector/s:	s22 (Lead), s22 (Co-inspector), s22 (Co-inspector)
Inspection finding summary:	0 Critical Deficiencies 2 Major Deficiencies s22
Date report issued to sponsor:	s22 2023
Reference:	s22

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Introduction

s22 was selected for a routine inspection as part of the TGA's Pharmacovigilance Inspection Programme (PVIP); all acronyms used in this report are listed in **Appendix III**. The purpose of the inspection was to review compliance with currently applicable Australian pharmacovigilance (PV) regulations and guidelines. In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021) (*Pharmacovigilance Guidelines*)
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

Company background:

s22 is an affiliate of s22 a global s22 company headquartered in s22 s22 In company standard operating procedures (SOPs), the affiliate is also ref to as s22 The sponsor employs approximately s22 employees across Australia and specialises in s22 products across s22 product areas: s22 and s22

Pharmacovigilance (PV) activities performed by s22 included:

- compilation of Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs)
- signal detection and management
- global literature search/review.

PV activities s22 to s22 and s22 included Individual case safety report (ICSR) intake, processing and some reporting to the TGA.

In s22 Medical Information (MI) and PV services were transitioned from the sponsor to the s22 located in s22 who performed the following PV activities:

- Local literature search and review
- Reconciliations
- Case intake
- Case follow up
- Serious adverse reaction (SAR) reporting to the TGA.

The PV team in Australia is composed of s47G(1)(a) sponsor employees:

- s47G(1)(a), who is also the Qualified Person Responsible for Pharmacovigilance in Australia (QPPVA)
- s47G(1)(a), who is also the Australian Pharmacovigilance Contact Person (A-PVCP) and s47G(1)(a) in Australia as defined in s22
- s47G(1)(a)

PV activities performed by this team included:

- PV training
- Ensuring implementation of appropriate safety reporting processes
- Assessment and submission of significant safety issues (SSI).

The Regulatory Affairs team in Australia consists of approximately s22 employees and were responsible for the submission of PSURs, RMPs and safety variations to the TGA.

s22 sponsor s22 registered medicines in the Australian Register of Therapeutic Goods (ARTG) for supply in Australia. s22 of these medicines are provisionally registered s22 Within the sponsor product portfolio, there are s22 products requiring RMPs and s22 products with ongoing PSUR submissions to the TGA. s22 sponsor products had inclusion in the Black Triangle Scheme applied as a specific condition of registration.

s22 products (s22 individual ARTG entries) were also promoted and distributed in Australia by s22 a third-party pharmaceutical company. s22 patient support program (PSP) and a number of market research programs delivered by third party vendors were ongoing in Australia. s22 post-authorisation studies sponsored by the sponsor were ongoing in Australia at the time of the inspection.

Brief report of the inspection activities undertaken

Scope of inspection

The inspection was conducted remotely via videoconference and included a review of both local and global PV systems. Company personnel from Australia, s22 attended the inspection via videoconference.

The inspection was conducted through interviews and review of documents, including searches of PV, MI and product quality complaint (PQC) databases. The PV topic areas reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as **Appendix II**) and included a review of:

- the collection, management and reporting of spontaneous and solicited adverse reaction (AR) reports
- ongoing safety evaluation and the management of SSIs
- the management of reference safety information (RSI)
- the management of PV post-approval commitments (PAC)
- the role of the A-PVCP and QPPVA
- the quality management system (QMS).

Documents submitted prior to the inspection

The company submitted an 'Australian Pharmacovigilance System Summary' (APSS) document on s22 s22 to assist with inspection planning and preparation. Other specific documents including PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the company prior to the inspection.

Conduct of the inspection

In general, the inspection was conducted in accordance with the Inspection Plan (attached as **Appendix II**).

Tabulated Summary of Inspection Deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing and reporting ARs and special situation reports received from spontaneous and solicited sources, were reviewed during the inspection. This included a review of all Australian reports received by the company during s22 When required, the narrative and source documentation for specific cases were analysed.

	Deficiencies related to the s22 and reporting of ARs are described in s22 and Major Deficiency 2 respectively.
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of company products were reviewed during the inspection. s22
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the inspection. Deficiencies related to the management and reporting of SSIs are described in Major Deficiency 1.
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the inspection. s22
Management of PAC	The procedure for managing PV PAC, including submission of PSURs, maintenance of RMP documents and implementation of RMP commitments, was reviewed during the inspection. s22
Role of the A-PVCP and QPPVA	During the inspection, the roles and responsibilities of the A-PVCP and QPPVA were reviewed. s22
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and SOPs, was reviewed during the inspection. s22

List of deficiencies identified during the inspection

Critical deficiencies

Nil critical deficiencies were identified during the inspection.

Major deficiencies

1. Deficiencies in management and reporting of SSIs

1.1. Late notification to the TGA of SSIs

In accordance with the *Pharmacovigilance Guidelines*, significant safety issues **MUST** be reported as soon as possible but no later than 72 hours of you receiving notice of them.

A review of 12 SSIs submitted to the TGA in the period from s22 , revealed two examples of delayed SSI notifications to the TGA.

The examples concerned s22 and the SSI assessments were conducted by the local PV team on day 21 and day 11 respectively, following the date of first local awareness. The subsequent notification to the TGA occurred on the same day of the sponsor assessment resulting in delays of 18 and 8 days respectively. The examples are described in the table below.

Product	Description of SSI	Date of first local awareness (Day 0)	Date of SSI assessment	Date of notification to the TGA	Time from local sponsor awareness (Day 0) to notification to the TGA (days)	Sponsor rationale for the delay
s22					21	The SSI was communicated from global office to the local Regulatory Affairs staff as a s47G(1)(a) . The staff member did not identify that this update also constituted an SSI and there was a delay in notifying local PV team.
					11	The SSI was communicated from global office to the local Regulatory Affairs staff who was on leave at the time and the email was not forwarded to the individual nominated in the out of office message. Therefore, there was a delay in notifying the local PV team.

1.2. Failure to identify SSIs from safety-related actions imposed by a Comparable Overseas Regulator (COR)

In accordance with the *Pharmacovigilance Guidelines*, a safety issue leading to international regulatory action is considered to be significant and hence reportable regardless of whether you agree with the recommendations and conclusions of the international regulator. Significant safety issues **MUST** be reported as soon as possible but no later than 72 hours of you receiving notice of them. To notify us in writing of significant safety issues with your medicine on the ARTG, submit your report to the PSAB Signal Investigation Coordinator.

The review of a sample of safety issues received by the sponsor revealed three examples which fulfilled the Australian definition of SSI that were not assessed by the local PV team and not notified to the TGA Signal Investigation Coordinator as an SSI. Details of the examples are described in table below.

Product	COR	High Level description of the signal/safety issue	Date of first local awareness (Day 0)	Sponsor justification for not notifying the TGA
s22				The s47G(1)(a) team provided the safety related action to the local regulatory affairs (LRA) team. The LRA team notified the issue to the Prescription Medicine Authorisation Branch of the TGA. However, they did not notify the local PV team for SSI assessment. On s22 the A-PVCP contacted the TGA SI Coordinator about these s22 safety issues in the context of the safety issues being potential SSIs and retrospectively notified the TGA s22
				The signal was not assessed by local PV team for SSI assessment. The signal was assessed by the global s22 team as not qualifying as an Emerging Safety Issue and that the Benefit/Risk balance remained unchanged. Subsequently, the s47G(1)(a) update was classified as s47G(1)(a) and was notified to the local Regulatory Affairs team as per the process described in s47

1.3. Delayed communication of SSIs from global company to local sponsor

In accordance with the *Pharmacovigilance Guidelines*, the TGA recognise that safety information may be received and processed by your global counterparts before it is disseminated to the local affiliates in Australia for reporting to us. We expect you to have clearly documented internal procedures in place that **ensure expedited communication** of significant safety issues from the global personnel to your relevant Australian personnel for

> reporting (…) Substantial or inappropriate delays between the global and Australian notification may be considered non-compliance with regulatory reporting timeframes.
> The Pharmacovigilance obligations of medicine sponsors - Frequently asked questions, published on the TGA website elaborates, if activities related to ongoing safety evaluation are conducted outside of Australia (for example, global headquarters, business partner, global pharmacovigilance vendor), then the TGA expects that Australian-based personnel (the Australian pharmacovigilance contact person or Qualified Person for Pharmacovigilance in Australia) are **urgently notified** of any safety issue that meets the definition of an SSI. Significant delays are considered unacceptable and pose a risk to public health.

A review of the SSIs notified by the sponsor to the TGA in the period from s22 revealed nine SSIs notified by s22 to the local sponsor company within a timeframe more than seven days, following the date of first global personnel awareness. Details of the examples are described in **Appendix IV**.

It is acknowledged that, once these issues were assessed, they were notified to the TGA as an SSI on the same day, except for examples 1 and 6. However, the timeline for the notification from the global team represented non-compliance with regulatory reporting timeframes for all examples. Sponsor management of examples 1 and 6 is discussed in **Major Deficiency 1.2**.

1.4. Deficiency in the process for communication of safety issues to local sponsor

> In accordance with the *Pharmacovigilance Guidelines*, A significant safety issue is a new safety issue or validated signal considered by you in relation to your medicines that requires urgent attention of the TGA.
> Other examples of significant safety issues include safety-related actions by comparable international regulatory agencies such as
> – the withdrawal or suspension of the medicine's availability
> – the addition or modification, for safety reasons, of a contraindication, warning or precaution statement to the product information or label
> – the modification or removal, for safety reasons, of an indication
>
> A safety issue leading to international regulatory action is considered to be significant and hence reportable regardless of whether you agree with the recommendations and conclusions of the international regulator.
>
> The TGA recognise that safety information may be received and processed by your global counterparts before it is disseminated to the local affiliates in Australia for reporting to us. We expect you to have clearly documented internal procedures in place that ensure expedited communication of significant safety issues from the global personnel to your relevant Australian personnel for reporting (…) Substantial or inappropriate delays between the global and Australian notification may be considered non-compliance with regulatory reporting timeframes.
>
> The QPPVA needs to have adequate understanding of the Australian and global pharmacovigilance processes in order to allow them to have effective oversight of the entire pharmacovigilance system.
>
> Where you have a global parent company, you need to be confident that your SOPs will ensure you become aware of international safety information and regulatory actions in a timely manner.

Processes that governed the sharing of safety issues with the local sponsor did not ensure the sponsor became aware of international safety information and regulatory actions in a timely manner.

The sponsor informed that safety signals classified as s47G(1)(a) were communicated to the sponsor immediately, within s47G(1)(a) following awareness s47G(1)(a)

s47G(1)(a) were communicated to the sponsor s47G(1)(a) Additionally, the sponsor received all company assessed signals s47G(1)(a) This included s47G(1)(a)

Appendix s47 of s47 outlined the timeframe for s22 assessment of signals as follows:

Company Classification / Company Priority	Time to Signal Validation (days from signal identification)	Time to complete overall Signal Assessment, including final decisions on conclusion, outcomes, and planned actions (days from signal validation decision)
s47G(1)(a)		

The sponsor explained that if a regulatory authority requested a shorter timeframe, the requested timeframe would be followed.

Since the SSI assessment responsibility lay solely with the local sponsor company, the process allowed for significant delays of the SSI assessment s47G(1)(a) A s47G(1)(a) report of s47G(1)(a), shared with the sponsor upon s47G(1)(a) was not considered timely notification of s47G(1)(a) s22 to the local sponsor company.

A safety issue leading to international regulatory action is considered significant and hence reportable regardless of the sponsors agreement with the recommendations and conclusions of the international regulator. These safety issues should undergo SSI assessment at the time of receipt of the request from COR, and not at the time of conclusion of internal signal assessment.

Deficiencies in the timeframe of communication from s22 to the local sponsor company, s47G(1)(a) were identified during inspection as discussed in **Major Deficiency 1.3**.

1.5. Deficiencies in the procedures for the SSI assessment of safety issues

> In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOP) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

Examples were identified where the sponsor's written procedures for SSI management were incomplete in relation to SSI assessment. Specifically, regarding sponsor procedure, s47

- There was no description of the routine s47G(1)(a) review of the s47G(1)(a) as a required activity to identify and assess SSIs. The inspector noted that Global PV was listed as a potential source of SSI but it did not describe the communication of the safety signals to the local sponsor via the s47G(1)(a).
- s47 stated that the s47G(1)(a) will ensure that "s47 ." The local s47 did not reference s47 and did not reference this s47G(1)(a) and s47 did not outline any responsibilities for the sponsor towards the

s47G(1)(a)

In summary, responsibilities and timelines for sponsor actions including the retrieval and assessment of safety issues in the s47G(1)(a) were not documented in any SOP at the time of the inspection.

2. Deficiencies in reporting SARs to the TGA

> In accordance with the *Pharmacovigilance Guidelines*, all serious Australian adverse reactions **MUST** be reported to the TGA within 15 days of receipt by the sponsor.

2.1. Non-submission of SAR reports to the TGA

During the inspection, a review of Australian valid cases received to the sponsor between s22 revealed s22 serious cases that had not been reported to the TGA by the sponsor. Any cases with a report source of Regulatory Authority were excluded from this review. Further details of the cases are provided in **Appendix V**.

2.2. Non-submission of SAR reports received from s22

During the inspection, two valid SAR reports were revealed that were received to the sponsor from the s22 on s22 entered into the sponsor safety database but not reported to the TGA. Details of the cases are outlined in the table below.

Case Id / Case type	Date Received by Company (Day 0)	All Suspect Products (generic name)	Events (Serious & non-serious; MedDRA PT)	All report sources	Reporter Causality / Company Causality (case level)	Sponsor rationale for no submission to the TGA
s22				Other Health Professional [Regulatory Authority], Contact [Regulatory Authority]	Yes / Unknown	No reports scheduled for Australia. Received via s22
				Other Health Professional [Regulatory Authority], Contact [-]	Yes / Unknown	Report scheduled but marked for non-submission. Received from s22

Although it was confirmed that these two reports were received to the TGA from the s22 and entered into the TGA Database of Adverse Event Notifications, these cases should still have been reported to the TGA by the sponsor following receipt and case processing. Regardless of whether the s22 reports adverse event s22 cases to the TGA or not, the TGA reporting obligations for sponsors do not change. No agreement between the

sponsor and the s22 was provided by the sponsor that specified the responsibility for reporting to the TGA.

Furthermore, it was noted that these two cases were recorded with a source of "Regulatory Authority", and this was incorrect. The TGA is the regulatory authority for therapeutic goods in Australia, and these two cases were not received to the sponsor from the TGA.

It was also unclear why one report s22 was scheduled for submission when the other report received the same day, from the same source s22 did not schedule for reporting. The reporting rules should result in the same scheduling outcome for two serious valid cases with the same source and case type, received the same day.

2.3. Late submission of SAR reports to the TGA

A review of initial and follow up SAR reports with case type spontaneous or post marketing surveillance, submitted to the TGA in a 2-year period between s22, revealed 31 (s22) late submissions out of a total of s22 submissions. The delays ranged from 1 to 173 days. Further details of these cases are provided in **Appendix VI**.

All 31 late submissions had a reason for delay recorded in the sponsor safety database which comprised 12 different reasons for lateness. The most frequent reason was "s22" which was assigned to 13 cases. Of these 13 cases, the delay was either associated with receipt of an E2B negative acknowledgement upon the first submission attempt (n7) (refer to **Major Deficiency 2.4**), or late due to an Information Technology (IT) disruption (n6) during s22 which affected transmission of sponsor online adverse event report forms to the case processing team.

2.4. Delays in monitoring and action of E2B negative acknowledgements

During the inspection, delayed submissions of SAR reports to the TGA where the reason for the delay was associated with company receipt of E2B negative acknowledgements were reviewed (n8). Whilst all eight case reports were originally submitted to the TGA on time, the delayed submission was due to the sponsor delay in the reschedule and re-transmission of the reports, including case corrections where required, following receipt of the E2B negative acknowledgement. Further details of these cases are provided in **Appendix VII**.

For all eight cases, the negative acknowledgement was received to the sponsor on the same day of the first transmission. The timeframe for sponsor management of the negative acknowledgement, including resubmission to the TGA ranged from three to 36 days.

The sponsor was aware of these late submissions and had performed a root cause analysis and taken actions to correct and prevent reoccurrence. In summary, the sponsor informed that the numbers of negative acknowledgements to be resolve s22. The complexities associated with s22 resulted in the delayed handling this negative acknowledgement.

The sponsor introduced changes in s22 for managing negative acknowledgements:

- Process for monitoring and resolving E2B negative acknowledgements was transferred from s22 to s22. Dedicated s22 were assigned to manage E2b negative acknowledgements on daily basis.
- Two s22 staff involved in the negative acknowledgement process were transferred to s47G(1)(a) s22 in order to liaise with s22 on s47G(1)(a) issue resolution, provide training and transfer knowledge.
- s22 is monitoring that s22 had appropriately actioned negative acknowledgements received s47G(1)(a)

The sponsor also informed that negative acknowledgements were now organized and actioned by "due date" of each report, where the reports due the earliest (still on-time) are prioritized, followed by due dates further away. In addition, following the identification of a negative acknowledgement, case correction must be performed immediately and without any unnecessary delay. Whilst these timelines were not outlined in a current sponsor procedure, it is acknowledged that the sponsor provided a draft, new, 's22 ' which was approved but not published/effective at the time of the inspection.

Although the sponsor rationale described s47G(1)(a) it was noted that the late submissions of s22 described in this deficiency, occurred before s22 Specifically, late submissions to the TGA due to this issue occurred as early as s22 (refer to case s47G(1)(a) in **Appendix VII**) therefore the delay in the introduction of changes (from s22), was not considered to represent timely identification and correction of this issue.

It was noted that the Reason for Delay in the safety database was recorded as s22 for all cases described in this deficiency submitted s22 (n7), whereas the case submitted after s22 included "*Rescheduling due to failed e2b Acknowledgment*" as the reason for delay, therefore the categorisation of the reason for delay may have contributed to a delay in this issue being identified.

2.5. Submission of cases to the TGA with no AR (outcome only)

> In accordance with the *Pharmacovigilance Guidelines*, all reports of suspected serious adverse reactions should be validated before you submit your report to the TGA. If a report cannot be validated it should still be retained and recorded in your pharmacovigilance system. Invalid reports also include those where only an outcome or consequence, such as hospitalisation or death, has been reported, with no further information provided on clinical circumstance to consider it a suspected adverse reaction. Use your clinical judgement to determine whether it is a valid serious adverse reaction or could constitute a significant safety issue and must be reported—for instance, you should report unexpected sudden deaths where the reporter considers it related to the suspect medicine or clusters of drug-event pairs that may indicate a safety signal.

During the inspection, sponsor rationale for submission to the TGA of a sample of two cases with event term "Death" was requested. For both cases, the sponsor informed, "*Over-reported in error. The* s22 *team created an* s47G(1)(a) *and will nullify the report at TGA.*" Further details of the two cases are provided in the table below.

Case ID / Case type	Day 0	Serious?	Is the case HCP confirmed?	Product	Adverse Events (MedDRA PT)	Date reported to the TGA
s22		Y	N	s22	Death, s22	s22
		Y	Y		Death	

				s22		

2.6. Non-alignment of sponsor reporting rules to the Pharmacovigilance Guidelines

A review of the sponsor SAR reporting rules via E2B to the TGA implemented in the safety database was conducted during the inspection. The review revealed that a 7-day reporting rule was implemented for fatal (F) and/or life-threatening (LT) reports associated with a sponsor suspect product that was marketed. However, the *Pharmacovigilance Guidelines* do not require any 7-day reporting and a 15-day reporting timeframe is stipulated for serious reports, regardless of seriousness criteria.

The sponsor informed that the following reporting rules were current at the time of the inspection and that they would apply to report (source) type of marketed report types; s47G(1)(a) :

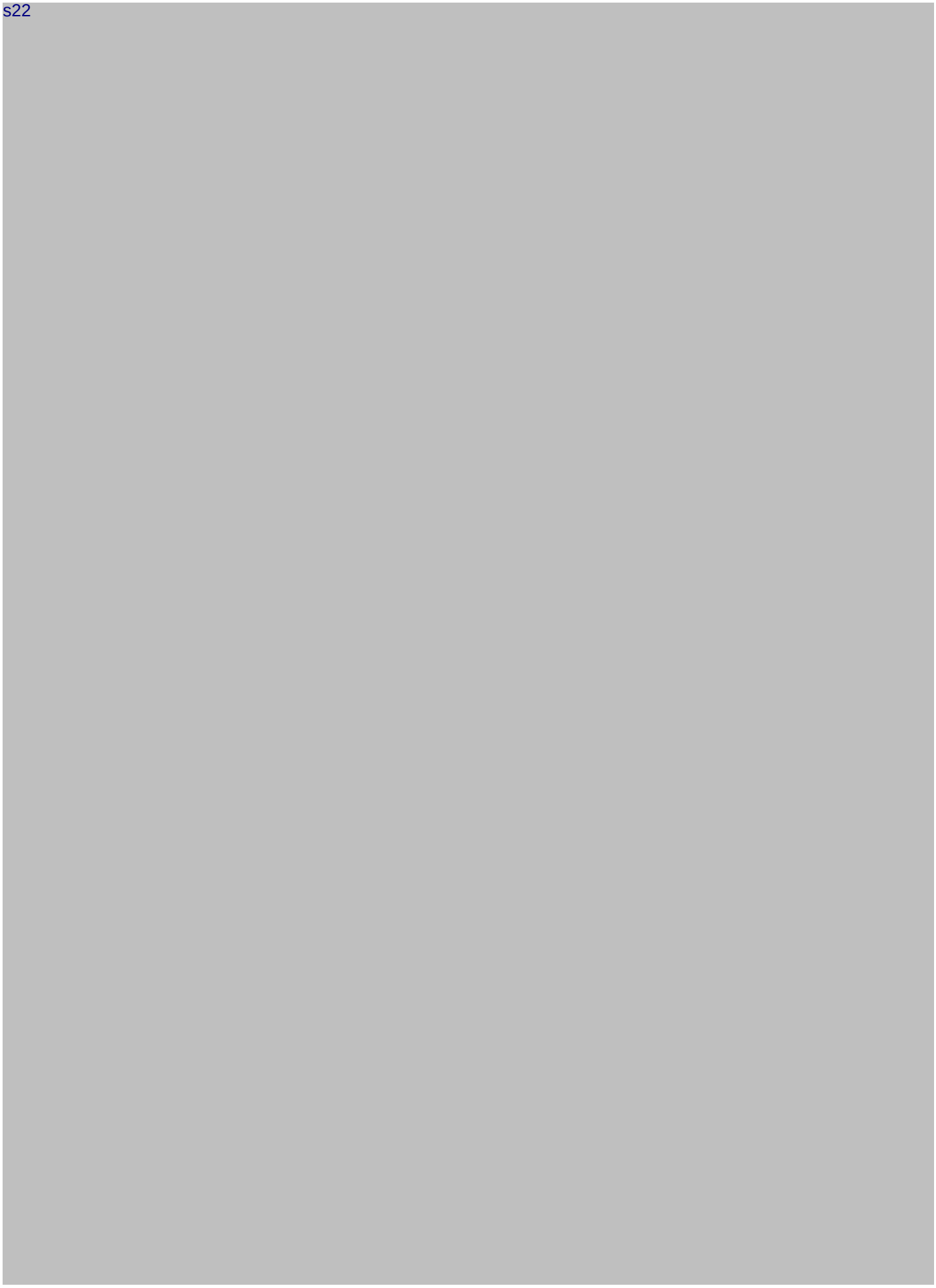
s47G(1)(a)

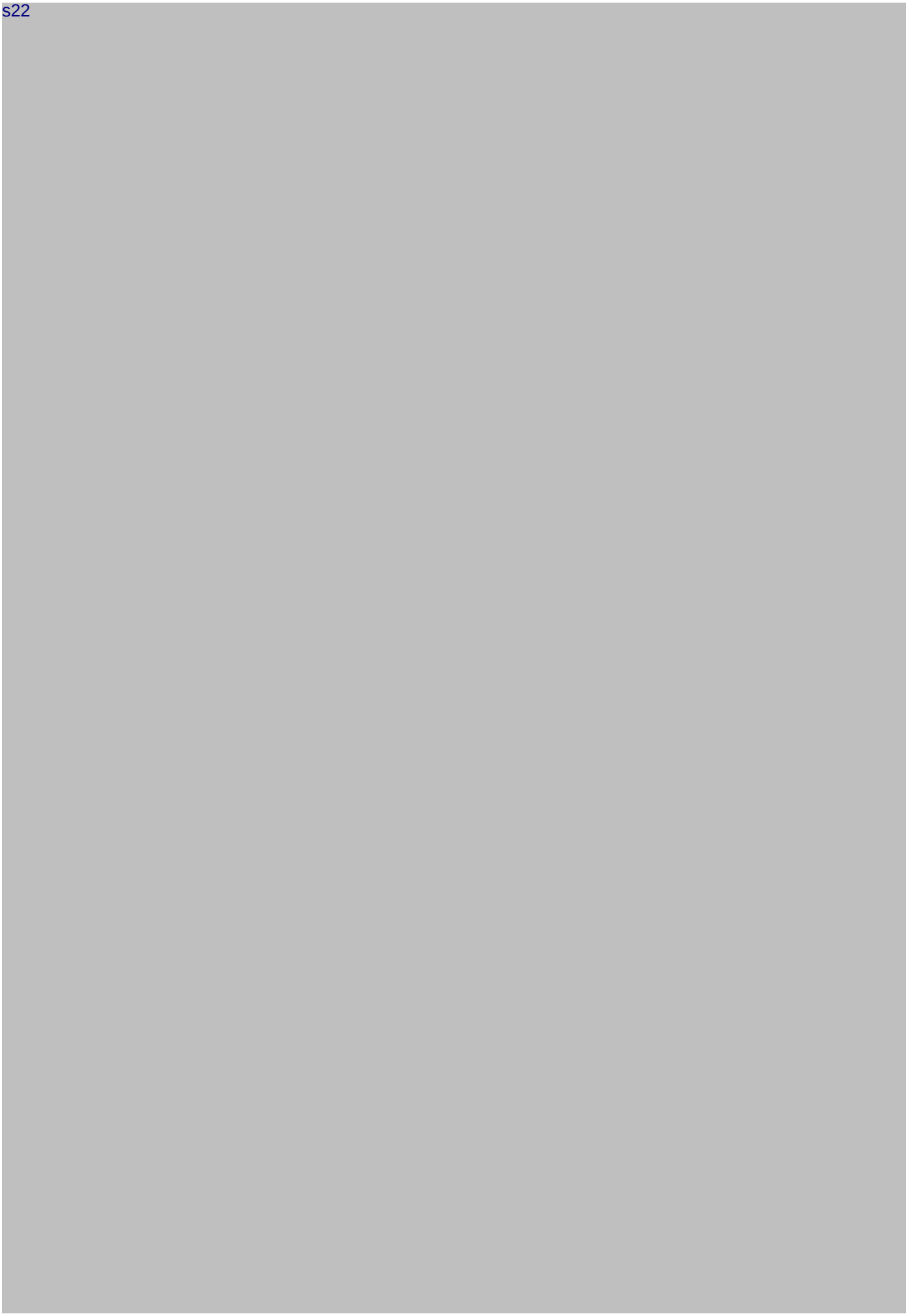
The sponsor provided two cases as examples of where these rules had been applied when reporting to the TGA as outlined in the table below.

Sponsor expedited reporting rule applied	Case ID	Source	Product	Event terms	Serious	Day 0	Date reported to the TGA
s22					Y	s22	
					Y		
s22							

s22

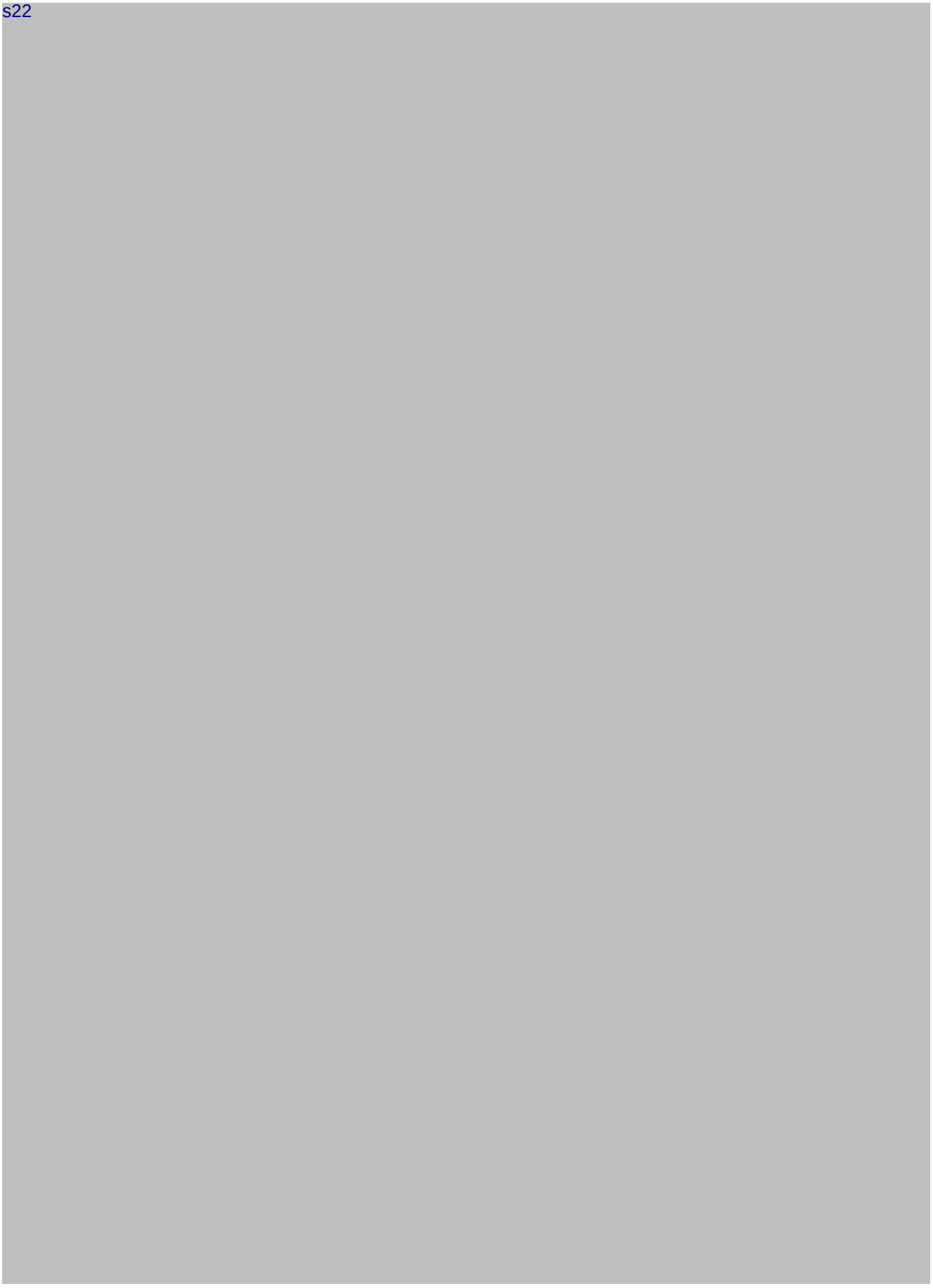
s22




s22

s22

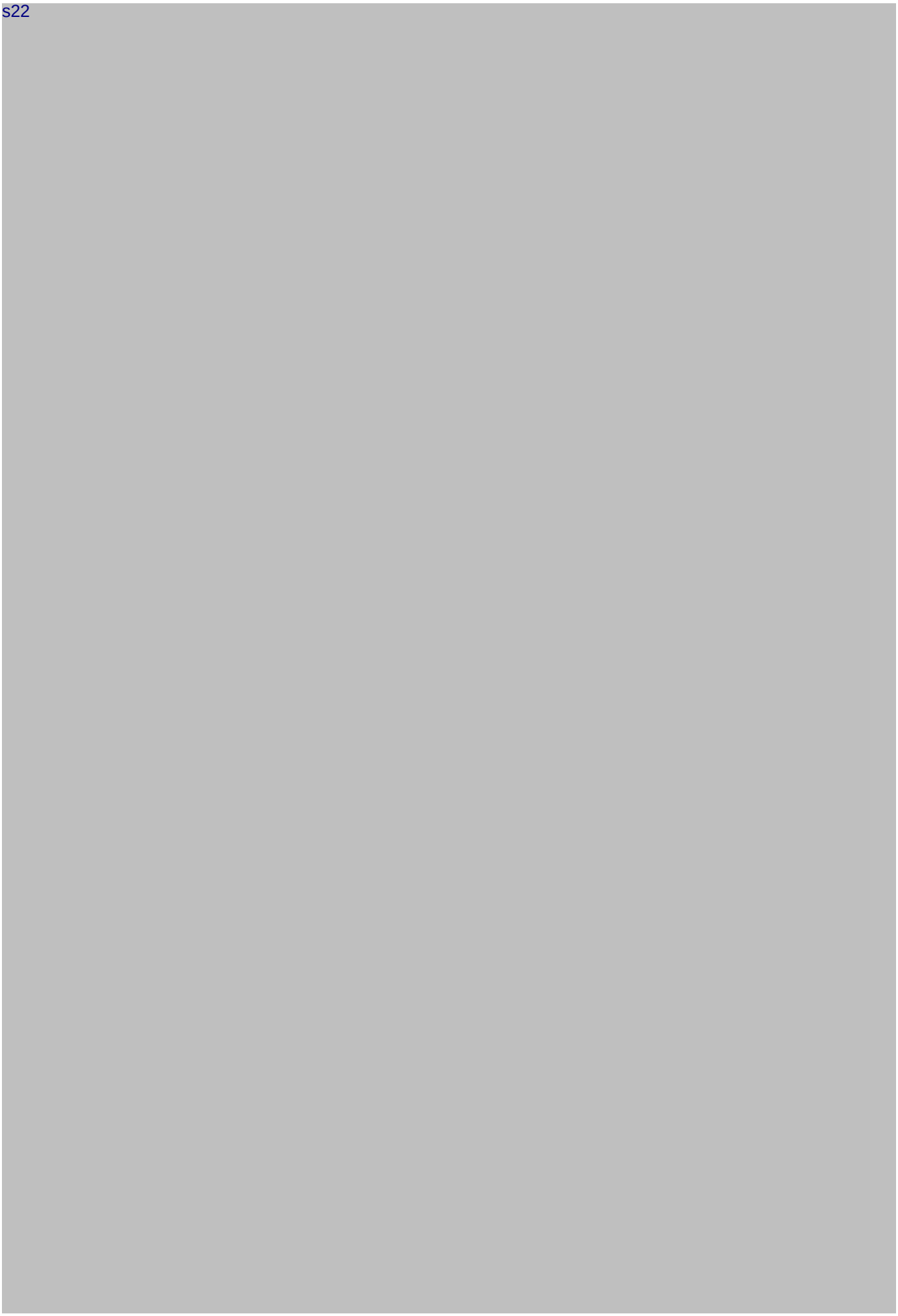
s22



s22

s22

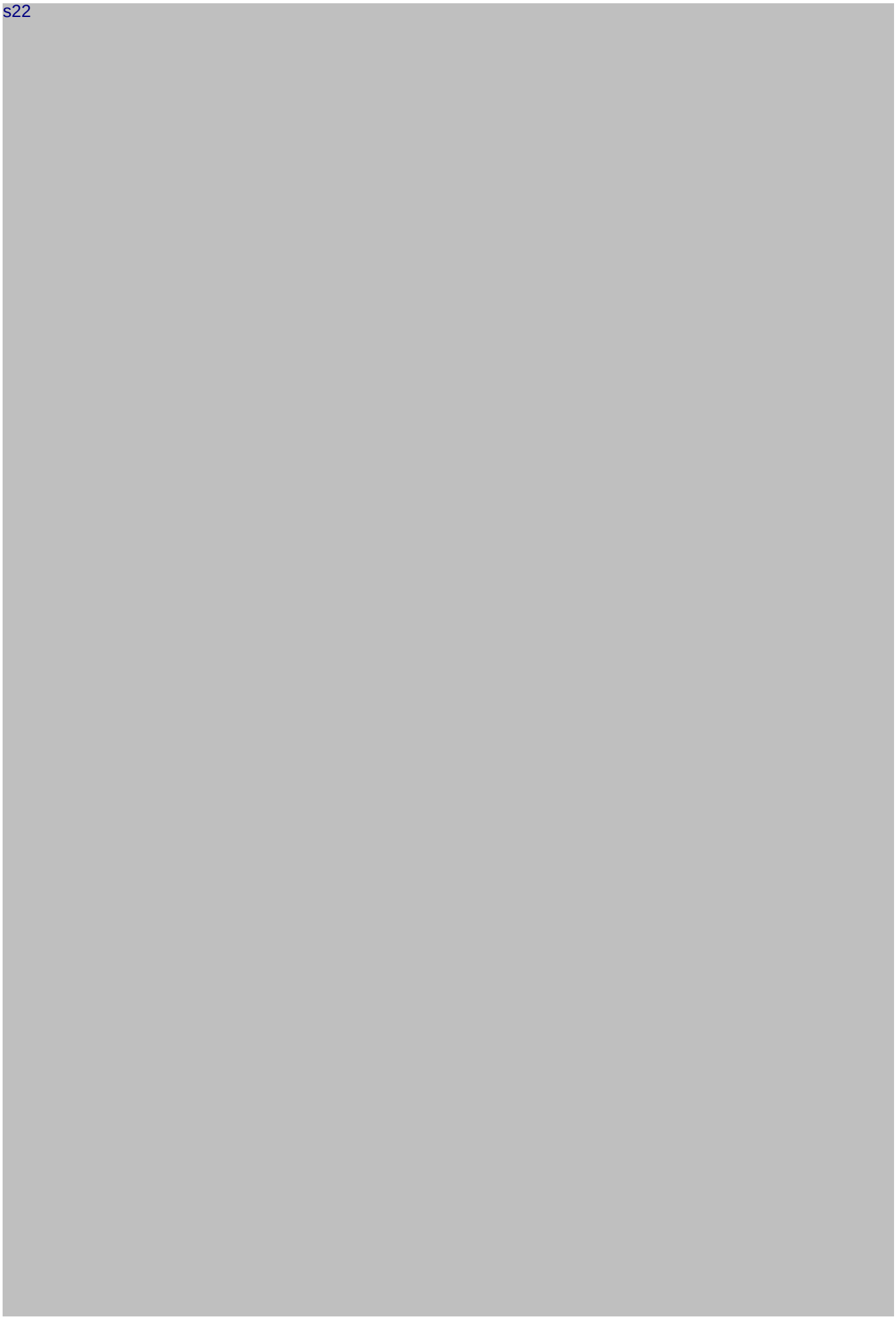
s22


s22

s22

s22

s22



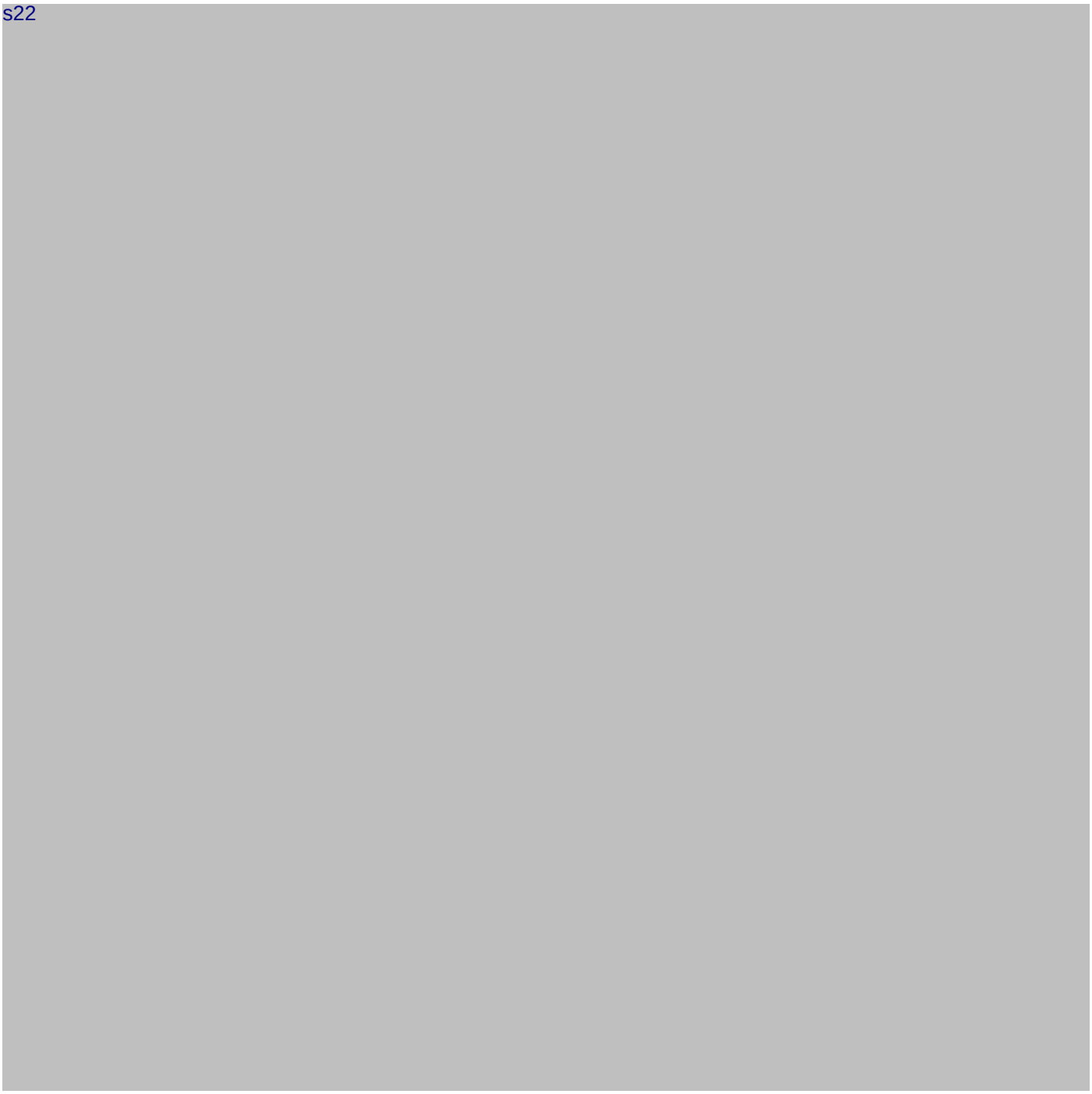
s22

s22

s22

s22

s22


s22

APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Pharmacovigilance Inspection Plan

Sponsor name:	s22
Sponsor address:	s22
Inspection type:	Routine systems-based (Remote)
Inspection dates:	s22
Inspectors:	s22 (lead inspector), s22 (co-inspector), s22 (co-inspector), s22 (observer)

Time (AEDT)	Activity	Staff involved
	PRE-INSPECTION CALL s22	
9am – 10am	Pre-inspection meeting • Inspection logistics • Testing audio, video, screen sharing • Q&A	TGA s22 Sponsor Staff s22
	DAY 1 s22	
9:30am	Opening meeting • Introductions • Attendance • Scope • Confirmation of Inspection Plan	TGA s22
	Company Presentation Overview of the company and pharmacovigilance system (30 mins)	Sponsor Staff

Time (AEDT)	Activity	Staff involved
		s22
10.30am	Case collection • Spontaneous sources of data (e.g. medical information enquiries, product quality complaints, literature, PV agreement partners, sales reps etc.) • Solicited sources of data (post-authorisation studies)	TGA s22 Sponsor Staff s22
12.30pm	**LUNCH**	
1.30pm	Review of procedures for the management of: Case entry Case management Follow-up Quality assurance Expedited reporting of adverse drug reactions to the TGA	TGA s22 Sponsor Staff s22
3pm-3.30pm	Case collection Solicited sources of data (programs)	TGA s22 Sponsor Staff

Time (AEDT)	Activity	Staff involved
		s22
3.30pm – 5.15pm	Post-approval pharmacovigilance commitments • Conditions of registration • RMPs • PSURs	TGA s22 Sponsor Staff s22
	DAY 2 s22	
9.30am	Maintenance of Reference Safety Information • Overview of the management of variation requests (Sponsor and TGA initiated) • Process for the updating PI and CMIs following the identification of new safety information • Implementation of PIs and CMIs following approval • Package inserts and label	TGA s22 Sponsor Staff s22
11.30am	Management and reporting of significant safety issues to the TGA	TGA s22 Sponsor Staff s22
1pm	**LUNCH**	
2pm – 4.45pm	Quality Management System • SOPs and other procedures	TGA s22

Time (AEDT)	Activity	Staff involved
	• Pharmacovigilance training • Record retention and archiving • Pharmacovigilance audits Role and responsibilities of the A-PVCP and QPPVA	s22 Sponsor Staff s22
	DAY 3 s22	
9am	Ad-hoc session with s22	TGA s22 Sponsor Staff s22
10am	Cut-off for document delivery for the closing meeting	-
3.30pm	Closing meeting	TGA s22 Sponsor Staff s22

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
AEFI	Adverse Event Following Immunisation
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
ATSI	Aboriginal and Torres Strait Islander (ethnicity)
CAPA	Corrective and Preventative Action
CMI	Consumer Medicine Information
COR	Comparable Overseas Regulator
CRM	Customer Relationship Management (system)
EMA	European Medicines Agency
ESI	Emerging Safety Issue
s47G(1)(a)	
F	Fatal
FDA	(US) Federal Drug Administration
s47G(1)(a)	
HCP	Health Care Professional
s47G(1)(a)	
ICSR	Individual Case Safety Report
IT	Information Technology
s47G(1)(a)	
LRA	Local Regulatory Affairs
MedDRA	Medical Dictionary for Regulatory Activities
MI	Medical Information
s47G(1)(a)	
PAC	Post-approval commitments
PI	Product Information
PMS	Post-Marketing Surveillance
PQC	Product Quality Complaint
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVIP	Pharmacovigilance Inspection Program
QMS	Quality Management System
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
RMP	Risk Management Plan
RSI	Reference Safety Information
SAS	Special Access Scheme
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
s22	
TGA	Therapeutic Goods Administration
s47G(1)(a)	

APPENDIX IV: MAJOR DEFICIENCY 1.3

No.	Product	High level description of SSI	Original Source	First Global company awareness date	First local sponsor awareness date	Time from global to local sponsor awareness (days)
1.	s22					68
2.						34
3.						31
4.						30
5.						27

6.	s22	26
7.		14
8.		13
9.		8

APPENDIX V: MAJOR DEFICIENCY 2.1

Case Id / Case type	Date Received by Company (Day 0)	All Suspect Products (generic name)	Events (Serious & non-serious; MedDRA PT)	All report sources	Reporter Causality	Company Causality (case level)
s22					Yes	Unknown
					Yes	Unknown
					Yes	Unknown
					Yes	Unknown
					Yes	Unknown
					Yes	Unknown
					Yes	Unknown

s22	Yes	Unknown
	Yes	Unknown
	Yes	Yes
	Yes	Unknown
	Yes	Unknown
	Yes	Unknown
	Yes	Unknown
	Yes	Unknown
	Yes	Unknown
	Yes	Unknown

s22	Yes	Yes

APPENDIX VI: MAJOR DEFICIENCY 2.3

Case Id / Case type	Date Received by Company (Day 0)	All Suspect Products (generic name)	Events (Serious & non-serious; MedDRA PT)	Submission date to the TGA	Delay (days)	Sponsor reason for delay
s22					6	s22
					2	

s22	2	s22
	2	
	5	
	22	
	13	

s22		s22
	33	
	2	
	2	
	2	
	20	
	20	
	19	

s22		s22
	46	
	172	
	173	

s22		s22
	9	
	1	
	49	
	12	
	1	
	14	

s22	2	s22
	12	
	14	
	14	
	14	
	14	
	15	
	7	

APPENDIX VII: MAJOR DEFICIENCY 2.4

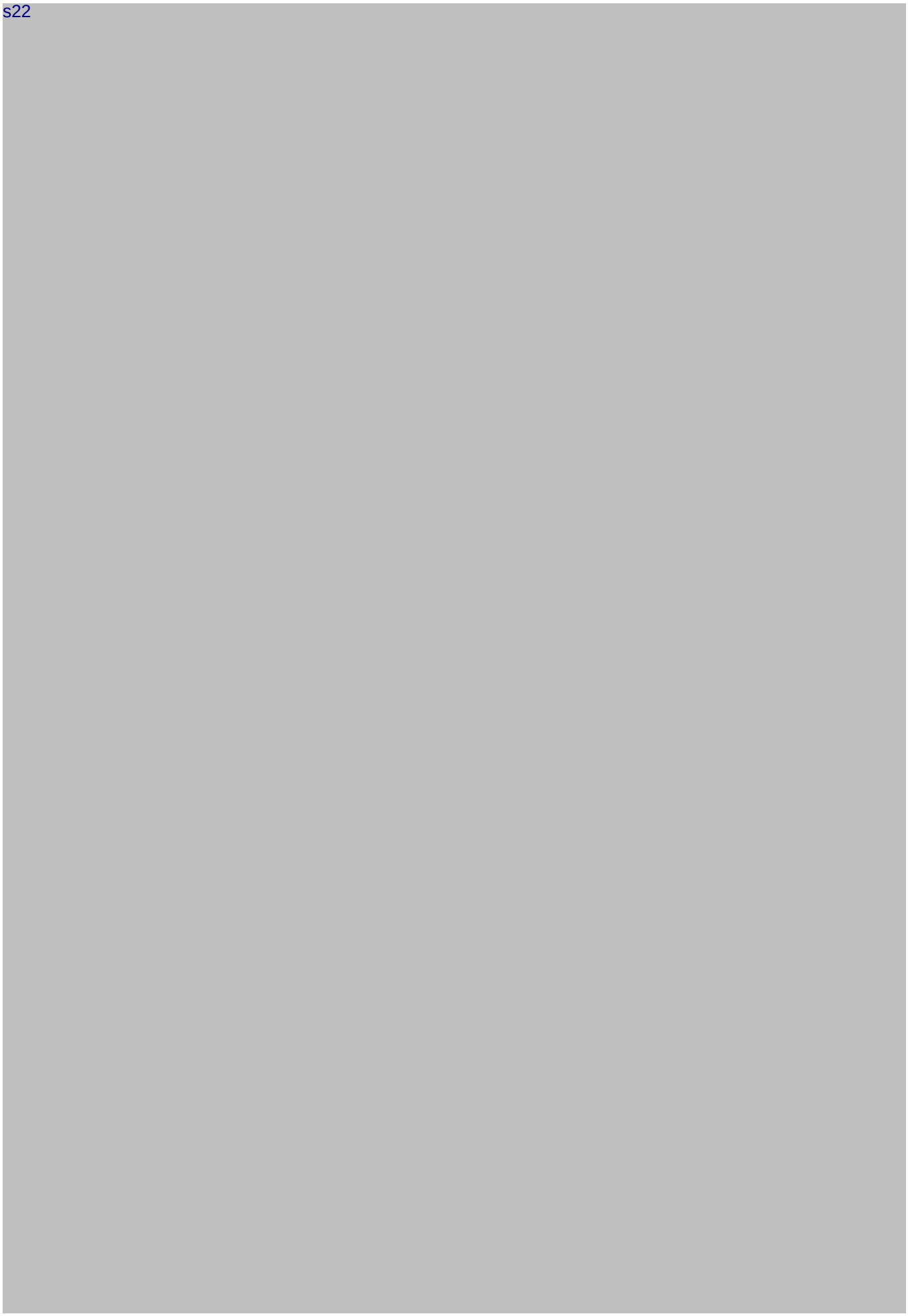
Case ID	Day 0	Product	Adverse Events (MedDRA PT)	Due date to the TGA	Date reported to the TGA (outcome of report transmission)	Timeframe for re-submission to the TGA following receipt of negative ack (days)
s22						36
						15
						3

s22	
	3
	14
	14
	3

s22	3

s22


s22


s22

s22

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22

RE: TGA Pharmacovigilance Inspection of s22

Please find attached the inspection report for the remote pharmacovigilance inspection of s22, conducted by the Therapeutic Goods Administration (TGA) on s22 2023.

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*. The purpose of the inspection was to assess compliance with the relevant pharmacovigilance legislation and guidelines and the conditions specified in the relevant approvals for registration or listing on the Australian Register of Therapeutic Goods (ARTG), and any subsequent variations.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021)
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as **Appendix I**).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Commitment Tracker.

For certain deficiencies, you may be requested to submit objective evidence of corrective or preventive actions after their completion dates.

Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed. In some circumstances, a re-inspection may be required to ensure completion of such activities.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Senior Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22 2023

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor address:	s22
Main site contact:	s22
Inspection type:	Routine, system-related inspection
Method of inspection:	Remote
Inspection scope:	To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines
Inspection date/s:	s22 2023
Inspector/s:	s22 (Lead), s22 (Co-inspector)
Inspection finding summary:	0 Critical Deficiencies 2 Major Deficiencies s22
Date report issued to sponsor:	s22 2023
Reference:	D23-5477220

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s22

Introduction

s22 was selected for a routine inspection as part of the TGA's Pharmacovigilance Inspection Programme (PVIP); all acronyms used in this report are listed in **Appendix III**. The purpose of the inspection was to review compliance with currently applicable Australian pharmacovigilance (PV) regulations and guidelines. In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021) (*Pharmacovigilance Guidelines*)
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

Company background:

s22 is located in s22 and employs approximately s22 employees across Australia. s22 sponsor s22 in the Australian Register of Therapeutic Goods (ARTG) for supply in Australia. s22 sponsor product is included in the Black Triangle Scheme (BTS), applied as a specific condition of registration and this product s22 also had a Risk Management Plan and Australian Specific Annex (RMP-ASA) with additional risk minimisation measures and ongoing Periodic Safety Update Report (PSUR) submissions to the TGA. The products sponsored and distributed by s22 span a range of therapeutic areas s22

s22 is an affiliate of parent company, s22 , based in s22 market and s22 products and s22 products across s22 . Prior to s22 was owned by s22 . s22 was established in s22 and the PV system was managed between relevant parties, s22 under the terms of a PV Agreement until the completion of the transition on s22 s22 . From this time to present, the PV system for s22 has been managed by s22 with oversight by the sponsor s22

s22 employees and contractors and the sponsor s22 comprise the s22 supports the provision of PV services for s22 is under the responsibility of the QPPVA (Qualified Person for Pharmacovigilance in Australia) - this role has been fulfilled by s22 since s22 . The QPPVA also fulfils the role of Australian Pharmacovigilance Contact Person (A-PVCP) for the sponsor.

In addition to the role of the QPPVA and A-PVCP, PV activities performed by s22 for the sponsor include:

- case processing and expedited reporting
- compilation of ASAs
- signal detection and management
- assessment and submission of significant safety issues (SSI)
- global and local literature search/review
- regulatory surveillance
- monthly screening of the TGA Adverse Events Management System via Public Case Details document request for one product
- reconciliations.

In addition to the role of the s22
provides s22
personnel which interface with PV. Aspects of the PV system managed by the sponsor include:

- PV training
- collection of solicited reports from Patient Support Programs (PSP), Market Research projects (MKR)
- Submission of PSURs, RMPs, ASAs and safety variations to the TGA
- maintenance of reference safety information (RSI).

At the time of the inspection, s47G(1)(a) PSPs and s47G Named Patient Program (NPP) were ongoing in Australia. Several MKR were conducted over the last two years. No post-authorisation studies sponsored by the sponsor were ongoing in Australia at the time of the inspection.

Brief report of the inspection activities undertaken

Scope of inspection

The inspection was conducted onsite on Day 1 and thereafter company personnel from Australia joined the inspection remotely via videoconference.

The inspection was conducted through interviews and review of documents, including searches of PV, MI and product quality complaint (PQC) databases. The PV topic areas reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as **Appendix II**) and included a review of:

- the collection, management and reporting of spontaneous and solicited adverse reaction (AR) reports
- ongoing safety evaluation and the management of SSIs
- the management of RSI
- the management of PV post-approval commitments (PAC)
- the role of the A-PVCP and QPPVA
- the quality management system (QMS).

Documents submitted prior to the inspection

The company submitted an 'Australian Pharmacovigilance System Summary' (APSS) document on s22
2023 to assist with inspection planning and preparation. Other specific documents including PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the company prior to the inspection.

Conduct of the inspection

In general, the inspection was conducted in accordance with the Inspection Plan (attached as **Appendix II**).

Tabulated Summary of Inspection Deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing and reporting ARs and special situation reports received from spontaneous and solicited sources, were reviewed during the inspection. This included a review of all Australian reports received by the company during s22. When required, the narrative and source documentation for specific cases were analysed.

	s22 [redacted]
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of company products were reviewed during the inspection. s22 [redacted]
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the inspection. s22 [redacted]
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the inspection. Deficiencies related to the management of Australian RSI are described in Major Deficiency 2.
Management of PAC	The procedure for managing PV PAC, including submission of PSURs, maintenance of RMP documents and implementation of RMP commitments, was reviewed during the inspection. Deficiencies related to the management of PAC are described in Major Deficiency 1.
Role of the A-PVCP and QPPVA	During the inspection, the roles and responsibilities of the A-PVCP and QPPVA were reviewed. s22 [redacted]
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and SOPs, was reviewed during the inspection. s22 [redacted]

List of deficiencies identified during the inspection

Critical deficiencies

Nil critical deficiencies were identified during the inspection.

Major deficiencies

1. Deficiencies in the management of PAC

1.1. Deficiencies in the management of EU-RMP

In accordance with the conditions of registration, sponsors **MUST** implement the version of the EU-RMP and RMP-ASA specified in the approval letter and any subsequent revisions as agreed with the TGA.

Furthermore, in accordance with the Risk management plans for medicine and biologicals Australian requirements and recommendations, Version 3.3, March 2019 sponsors **MUST** submit an updated RMP and/or ASA when we request it and whenever there is significant change, such as: when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.

For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the request of the TGA, then we recommended that the updated RMP/ASA **is submitted within 3 months of the change being accepted by the EMA.**

You should update your risk management plan when new information becomes available regardless of whether your product is marketed. **You should ensure that you always keep your RMP and ASA up to date for your own records** and because we may request an updated RMP from you at any time.

1.1.1. Deficiencies in the maintenance of the RMP-ASA for s22

During the inspection, it was revealed that to date, the sponsor did not submit any s22 EU-RMP updates to the TGA nor maintain the version of the RMP-ASA in relation to the updated EU-RMP, despite the EMA approval of numerous updates to the s22 EU-RMP over a period of more than four years.

The approval letter for s22 dated s22 stated:

s22

During the inspection, all versions of s22 EU-RMP updates since s22 were requested and details of the EMA approved updates are described in the table below.

EU- RMP version/date	Date of EMA approval	Date of notification to sponsor	Time taken for notification to sponsor (days)	High level summary of changes included
s22				

s22

The sponsor submitted two versions of the RMP-ASA to the TGA after the approval of s22 . Details of the RMP-ASA updates are described in the table below.

s22 ASA version	Associated EU-RMP version	Date of submission to the TGA	High level summary changes of changes included
s22			

These two updates to the ASA were mainly related to additional risk minimisation activities specific to Australia. However the sponsor had not reviewed the ASA, in the context of the EU-RMP updates approved by the EMA since version s47G(1)(a) Based on the dates of submission to the TGA, RMP-ASA version s47G(1)(a) and version s47G(1)(a) should have been associated with the updated EU-RMP version s47G(1)(a) which was approved by the EMA on s22 (before the submission of these ASA updates to the TGA).

The sponsor informed that EU-RMP updates for s22 were not communicated to the sponsor by s22 . The current Safety Data Exchange Agreement (*SDEA) between* s22 stated that, "s22 However, this wording did not provide a specific timeframe to s22 for their notification to the sponsor regarding EU-RMP updates.

Furthermore, the timeframes for notification of the EU-RMP version s47G(1)(a) and version s47G(1)(a) of s22 days and s22 days respectively, were not considered timely and therefore represented non-compliance with the SDEA. The sponsor explained that s22 had not provided notifications of any s22 EU-RMP updates subsequent to version s47G(1)(a) until s22 and this was likely due to changes in personnel at s22 .

1.1.2. Failure to submit updated EU-RMPs to the TGA

Of the updates approved by the EMA to the EU-RMP for s22 since the TGA approval of the product in s22 with EU-RMP version s47G(1)(a), the updates in version s47G(1)(a) and version s47G(1)(a) were significant and were required for submission to the TGA. As of s22 , the sponsor had not submitted these versions of the EU-RMP to the TGA and this represented delays of at least s22 days and s22 days respectively.

Product	EU-RMP version	High level description of changes	EU-RMP approval date	TGA submission due date (3 months from EMA approval date)	Delay (days)*	Sponsor reason for delay

s22	1242	s22
	26	Not requested

*Delay reflects the number of days at the time of inspector review on s22 2023.

1.2. Failure to update and submit the RMP-ASA following substantial changes to an additional risk minimisation activity

According to the guidance document *Risk management plans for medicine and biologicals Australian requirements and recommendations, Version 3.3, March 2019,* the sponsor must submit an updated RMP and/or ASA whenever there is significant change, such as: when an additional risk minimisation activity is ceased, added or substantially altered.

During the inspection it was revealed that an additional risk minimisation activity described in the RMP-ASA for s22 was substantially altered however this update had not been notified to the TGA via the submission of an updated ASA with the proposed changes to the TGA.

As described in s47 submitted to the TGA on s22 , the document s47G(1)(a) formed part of the s47G(1)(a) resources s47G(1)(a) . The supply of s47G(1)(a) resources, s47G(1)(a) , was one of the agreed additional risk minimisation activities first added in version s47G of the RMP-ASA submitted to the TGA s22 The sponsor confirmed during the inspection that the s47G(1)(a) was no longer supplied. The sponsor informed that alternatively, s47G(1)(a)

The discontinuation of the supply of the s47G(1)(a) was a significant change to the proposed additional risk minimisation activities in Australia and the ASA was required to be updated and submitted to the TGA to reflect the change.

1.3. Delayed PSUR submissions to the TGA

In accordance with the condition of registration, sponsor **MUST** submit PSURs to the TGA in line with the timeframes and frequency specified in the condition of registration.

In accordance with the *Pharmacovigilance obligations of medicine sponsors: Frequently asked Questions*; for products that are approved in the European Union (EU), the TGA will usually align the PSUR reporting requirements and timeframes with those required by the European Medicines Agency (EMA). In this case, the specific condition of registration will state that PSUR reports are to align with the current EU reference date (EURD) lists- external site, which are published on the EMA website. Sponsors are expected to provide PSURs to the TGA consistent with all elements described in the EURD list, including:
- PSUR submission frequency
- Data lock point
- PSUR submission due date (according to the timelines defined in GVP Module VII, Section A)

In accordance with *Guideline on Good pharmacovigilance practices (GVP) Module VII – Periodic Safety update report*, Section A; for PSUR covering interval up to 12 months (including interval of exactly 12 months); PSUR should be submitted within 70 calendar days of the data lock point.

During the inspection, three late PSUR submissions for s22 were identified. The delays in the submissions ranged from 17 to 202 days. Details of the delays are provided in the table below.

Product	Period covered by PSUR	Data Lock Point (DLP) of PSUR	Date of PSUR preparation	Submission due date to the TGA	TGA submission date (actual)	Delay (days)
s22						17
						202
						89

The submission due dates of PSUR reports to the TGA as tracked by the sponsor were requested but were not provided. The sponsor explained that "*It is unclear as to how long the sponsor has once the PSUR/PBRER is prepared, to being submitted to the TGA.*" However, according to the condition registration imposed in the approval letter for s22, dated s22 PSUR s22. The sponsor was therefore required to refer to the EU reference date (EURD) list that was current at the time of PSUR data lock point for the submission due date to the TGA and align the PSUR submission date accordingly.

1.4. Deficiencies in sponsor oversight of PAC

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

The QPPVA needs to have (...) effective oversight of the entire pharmacovigilance system.

The sponsor did not maintain a formal tracker of PAC to the TGA, including for the submission of PSUR and RMP updates. The sponsor informed that a reoccurring s47G(1)(a) entry for s47G(1)(a) years was entered into s47G(1)(a) to track the s22 PSUR submissions. No tracking was in place for RMP updates and RMP commitments.

During the inspection, it was revealed the s22 post-authorisation studies, first included in the current version of the s22 as part of the additional risk minimisation activities to be carried out in Australia, had not been implemented. Details of the studies are described in the table below.

Study Number	Study Name	Study Objectives
s22		

The sponsor explained that the study protocols were submitted to the RMP section of the TGA, on s22 s22 and, except for the acknowledgement of receipt of the ASA, they had not received any

further correspondence from the section regarding the acceptability of the protocols and the sponsor did not follow up with the TGA to date.

The sponsor confirmed that there was no standard procedure or tracking for the management and monitoring of additional risk minimisation activities, such as the activities described in the s22 . The lack of formal tracking and monitoring of PAC may have contributed to the delay in the implementation of the s22 studies.

The sponsor is ultimately responsible and accountable for compliance and completion of post approval commitments. If the sponsor had tracked PAC, the sponsor may have been prompted to follow up with the TGA regarding the acceptability of the proposed protocols and minimised the delay in the implementation of the s22 post-authorisation studies.

Sponsors are expected to implement SOPs and incorporate them into the QMS, including training on these procedures, to ensure prompt completion and oversight of PAC. Furthermore, without a comprehensive tracking system, it was not possible to verify sponsor and QPPVA oversight of compliance with PAC imposed by TGA for sponsor products.

1.5. Deficiencies in sponsor processes for RMP-ASA maintenance

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

We expect you to have an effective pharmacovigilance system.

During the inspection, no sponsor written process to outline responsibilities towards maintenance of RMP-ASAs were available.

Section s47 of SOP s47 , provided a high level description of the roles and responsibilities for the preparation, review, revision, and submission of RMPs. However, it did not define requirements, roles and responsibilities for maintenance of the RMP-ASA, beyond, "s47 " nor timelines for the submission of updates.

The current sponsor processes did not facilitate sponsor compliance with the requirement to monitor and submit relevant EU-RMP updates to the TGA and may have contributed to Major Deficiency 1.1 and 1.2.

2. Deficiencies in the management of RSI

2.1. Delay in updating Australian PI (after TGA approval)

In accordance with the conditions of registration, sponsors **MUST** lodge the approved PI with the TGA within 2 weeks of the date of approval of the variations.

During the inspection a delay of six days in the lodgement of the approved PI to the TGA Business Services (TBS) was noted for s22 Details are outlined in the table below.

Product (ARTG No)	Original source of the variation	High level description of the safety related change	Date of the TGA approval of the variation	Date approved PI updated to the TGA website	TGA approval to lodgement (days)	Delay (days)
s22	TGA	s22			20	6

s22			

2.2. Delay in updating Australian CMI (after TGA approval)

In accordance with the conditions of registration, if the related CMI documents needs to be updated as a consequence of the change to the approved PI, the sponsor must lodge the updated CMI with the TGA within 2 weeks of the date of the changed PI.

During the inspection a delay of 137 days in the lodgement of the CMI to TBS for s22 was noted. Details are outlined in the table below.

Product (ARTG No)	Original source of the variation	High level description of the safety related change	Date of the TGA approval of the variation	Date approved CMI updated to the TGA website	Approval to lodgement (days)	Delay (days)
s22	TGA	s22			151	137

The sponsor explained that internal comments were provided from the initial review of the updated CMI on s22. However, the review was not finalised internally until s22 which may have caused the delay.

2.3. Deficiency in RSI record keeping

Under paragraph 28(5)(ca) of the Act, you **MUST** retain records pertaining to the reporting requirements and safety for your medicine.

Under Therapeutic Goods Regulations 1990 (Regulation 15A), for the purposes of paragraphs 28(5)(ca) and (e) of *the Act*, a person in relation to whom a medicine is registered or listed must comply with the record-keeping requirements (if any) and the reporting requirements (if any) set out in the document published by the Therapeutic Goods Administration titled Pharmacovigilance Responsibilities of Medicine Sponsors, as in force from time to time.

According to the *Pharmacovigilance Guidelines*, **reference safety documents MUST** be retained indefinitely for the life of the medicine and for a period of 10 years after removal from the ARTG for registered medicines, and a period of 5 years after removal from the ARTG for listed medicines.

According to the *Pharmacovigilance Guidelines*, you **MUST** meet your pharmacovigilance reporting responsibilities for all the medicines you have registered or listed on the Australian Register of Therapeutic Goods (ARTG). This is regardless of their Australian marketing status—that is, whether they are currently available for purchase.

During the inspection, current RSI for a sample of sponsor products was requested. The sponsor was not able to provide the label and PI for s22

The sponsor explained that the product was acquired from s22 It is acknowledged that s22 however the requirements and recommendations of the *Pharmacovigilance Guidelines* apply to all sponsor products, regardless of supply status.

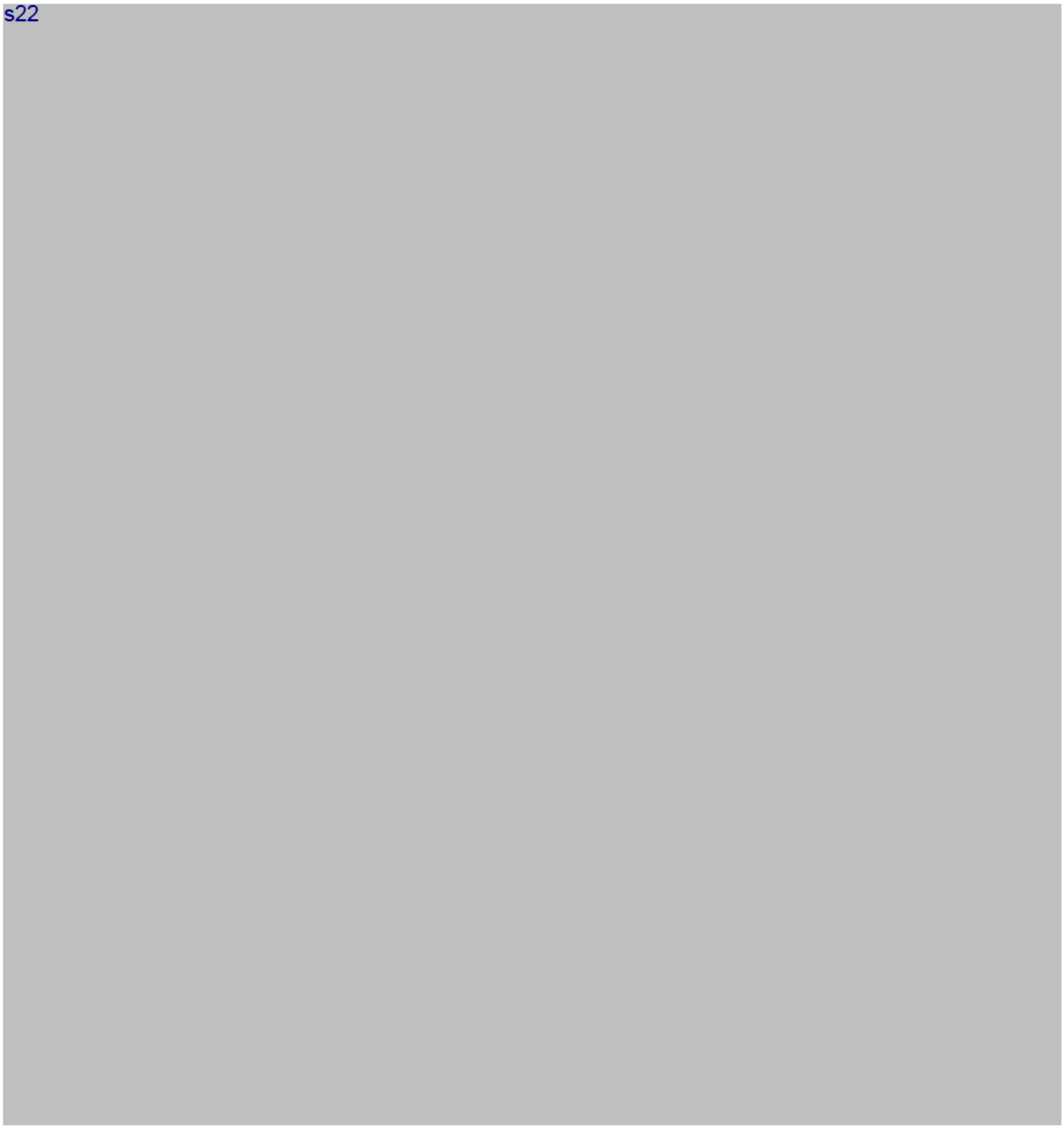
2.4. Failure to update the CMI available on a sponsor website

In accordance with the *Pharmacovigilance Guidelines*, sponsors are responsible for the safe use of their medicine. Timely communication and control of superseded reference safety information is critical in ensuring current safety information is available to sponsor's staff, as well as health professionals and consumers.

The CMI for s22 available on a sponsor website for Australian healthcare professionals was not the current version and was outdated by approximately two years and eight months. Furthermore, the CMI version on the website was missing two subsequent safety related updates.

On s22, the company website, s22 was accessed by the inspector to verify the currency of the RSI made available to Healthcare Professionals (HCP) who had registered on the website. The sponsor informed that the purpose of the website was s22. It was identified that the CMI version available under the "s22" section of the website was s22 and did not align with the current version of the CMI dated s22 that was available from the TGA website at the time of the inspection. Further details regarding the two versions of the CMI are provided in the table below.

Section of the CMI*	Content of CMI available on s22	Content of current CMI (Version s22)**	Summary of difference
s22			



*Heading of CMI based on format used for CMI Version

The sponsor informed that the team was notified when a PI and/or CMI update had been approved and would work in collaboration with the sponsor and teams for the review and approval of any related promotional material, including the website. The team was then responsible for the implementation of the updated content on the website.

The inspector requested the standard procedure that the team followed for the maintenance of the content of the website and it was not provided. The sponsor provided a high-level description of the SOP , described as the standard procedure for the management of promotional material. The sponsor informed that the SOP described,

However the version of the CMI available on the s22 website was out of date by more than 24 months (2 years and 8 months). This suggested that the timeline in SOP *VV-QUAL-31138* was not followed for the CMI on the s22 website.

To ensure the safe use of medicines, it is necessary that all RSI materials available to healthcare professionals, such as PI and CMI and educational materials available on the company's websites or other company owned platforms, are kept up to date. Using out-of-date RSI may result in provision of inaccurate information to prescribers or Australian public.

2.5. Deficiency in the company procedures for the management of RSI

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

During the inspection, examples were identified where the sponsor's written procedure for the maintenance of RSI was incomplete. The examples are outlined below and relate to current sponsor s47

Example 1)

s47 described that after the s47G(1)(a) team received advice of a potential label change, the team would assess its applicability to the local label and determine if a submission is required.

However, the procedure did not stipulate the requirement to document the rationale of the decision to either update or not update the Australian label. The sponsor informed that in practice the decision to not update the label was documented in the emails between s47G(1)(a) team and s47G(1)(a) team. Formal documentation of the decision was required to record evidence of the assessment.

Example 2)

s47 stated that after the TGA approval of the PI, Regulatory Affairs was responsible to send a copy of the finalised PI and CMI to s47G(1)(a) for publication.

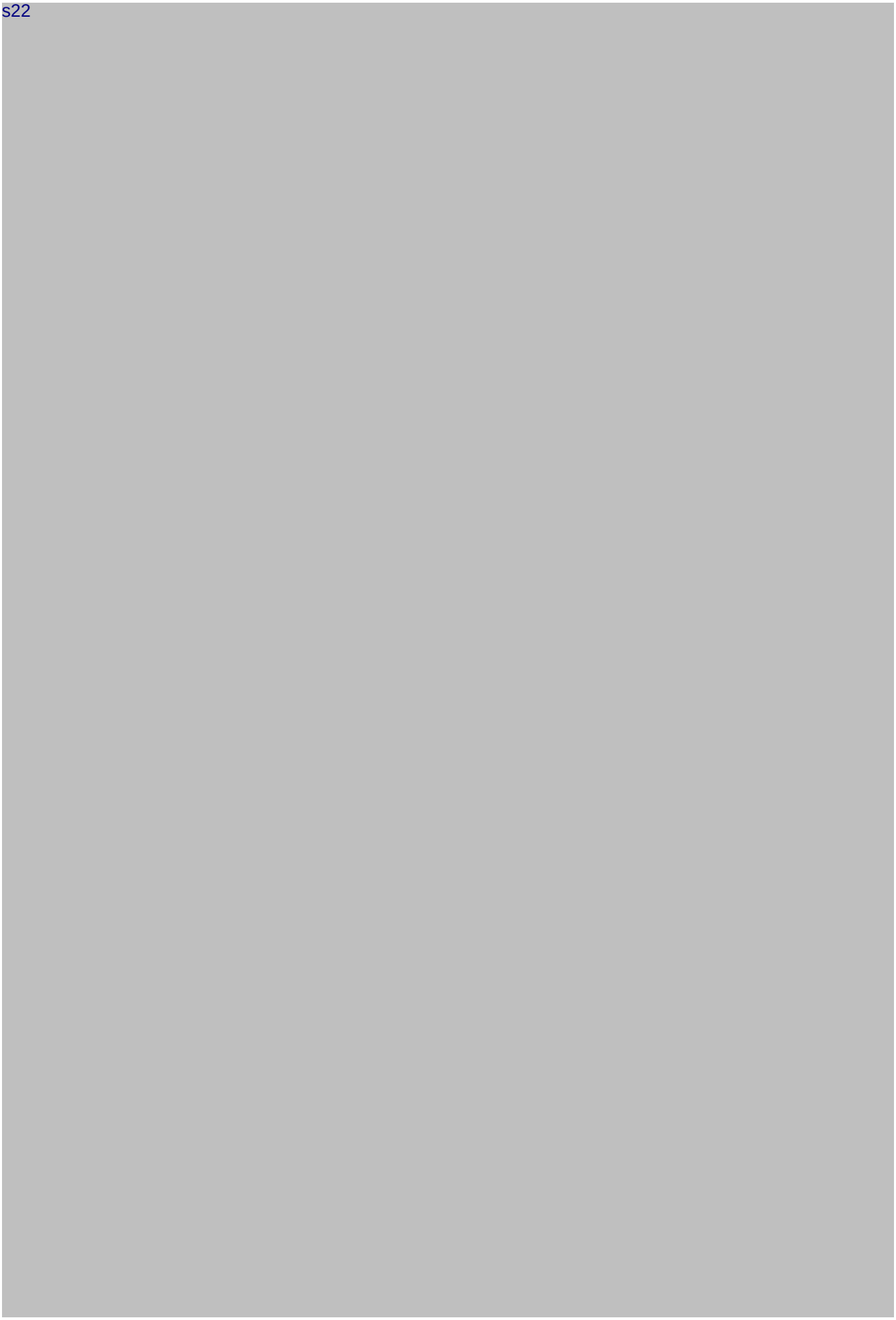
However, no timeline was stipulated in the procedure to ensure compliance with the regulatory two week timeframe. The sponsor also informed that they did not maintain a tracker for such post approval activities following the TGA approval of the PI for oversight of compliance, which may have contributed to the delayed PI and CMI lodgement discussed in Major Deficiency 2.1 and 2.2. It is acknowledged that the sponsor verbally confirmed their awareness of the regulatory timeframe during the inspection and affirmed that they aim to comply with the timeframe.

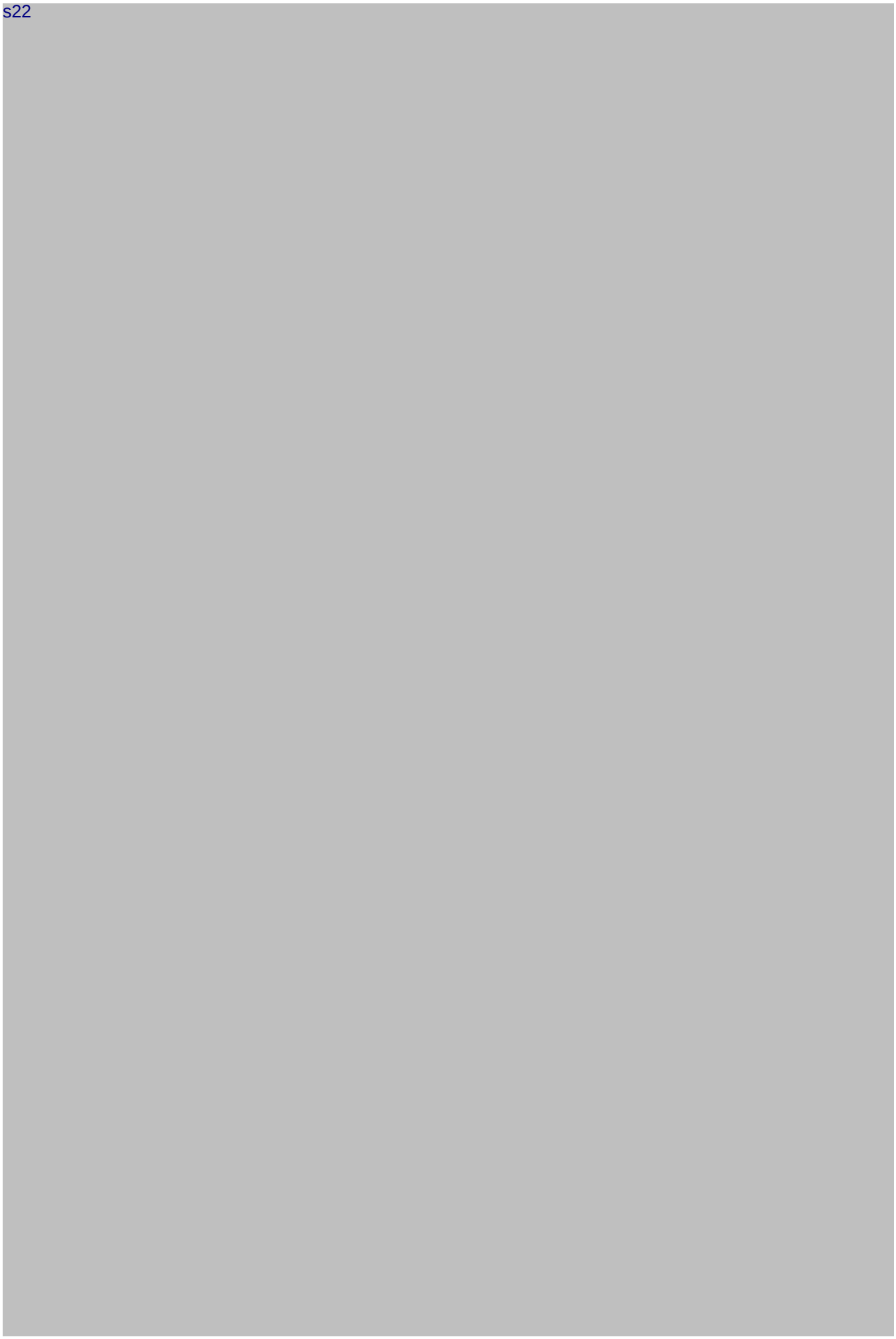
Example 3)

s47 stated that once approval from the s47G(1)(a) is received, s47G(1)(a) send a notification to s47G(1)(a) and s47G(1)(a)

However, during the inspection, the sponsor informed that the s47G(1)(a) team will send a notification to the s47G(1)(a) **teams**. The notification to the PV team facilitated QPPVA oversight over RSI management however this important stakeholder was not specified in the SOP. Please refer to s22

s22

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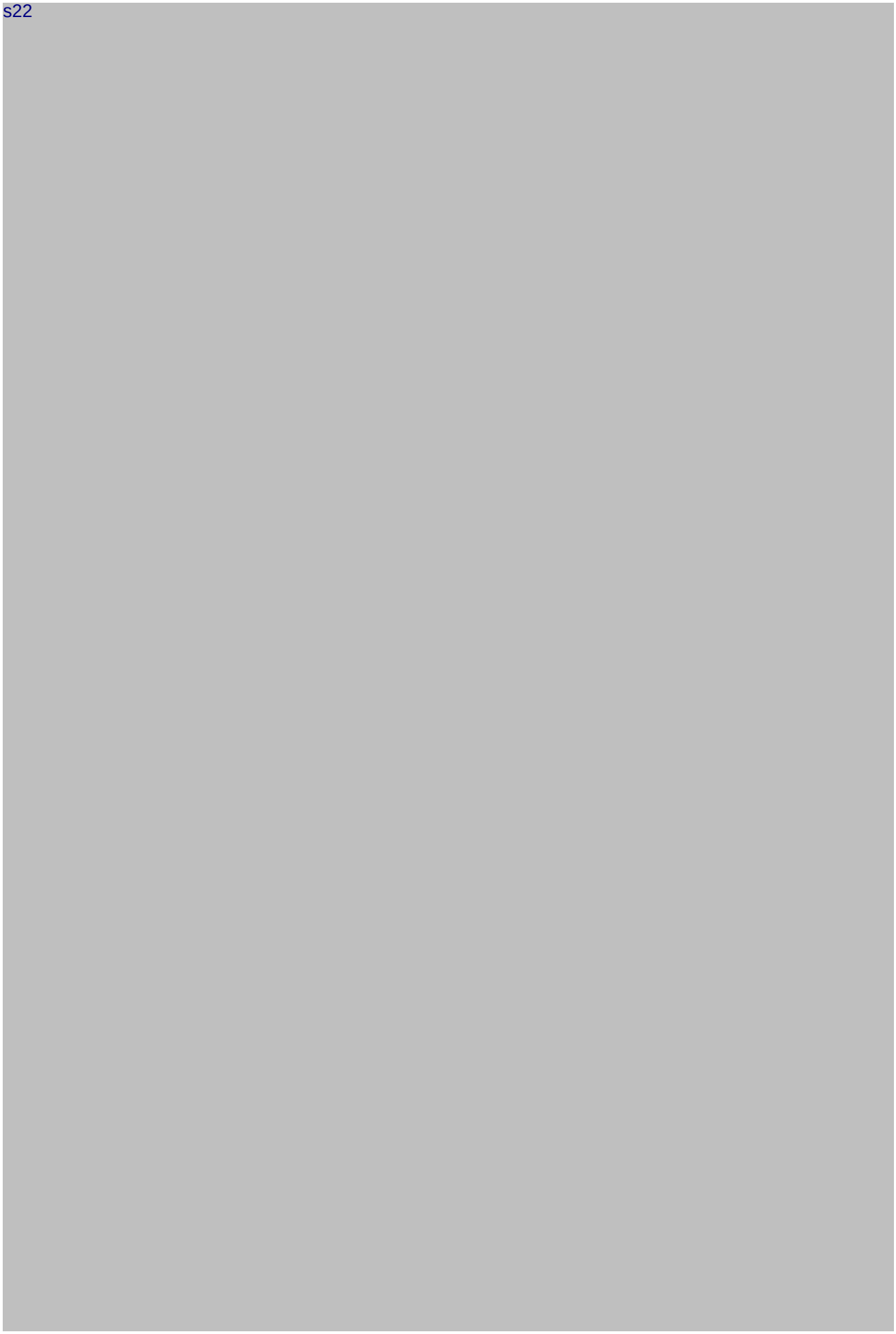
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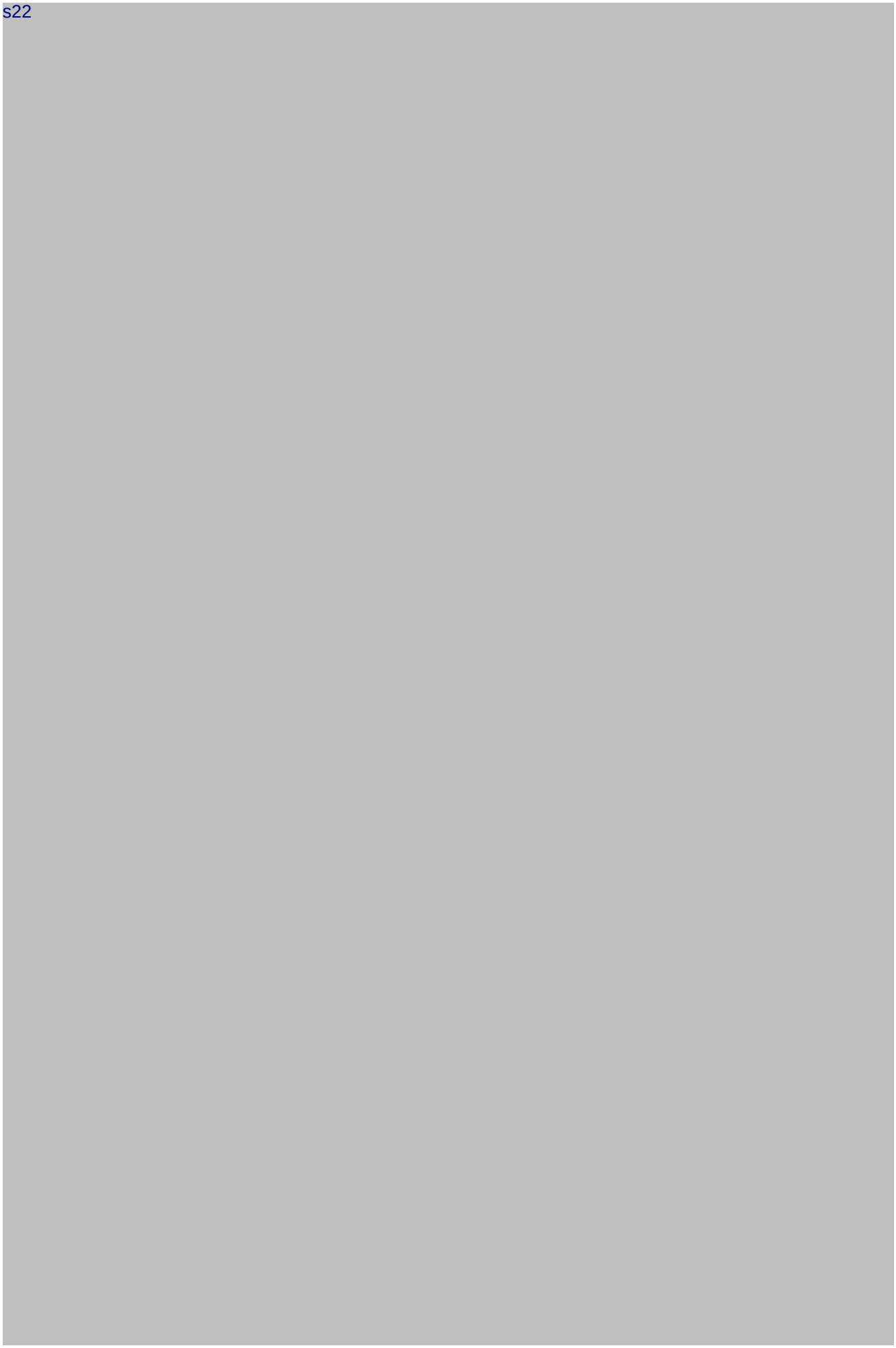
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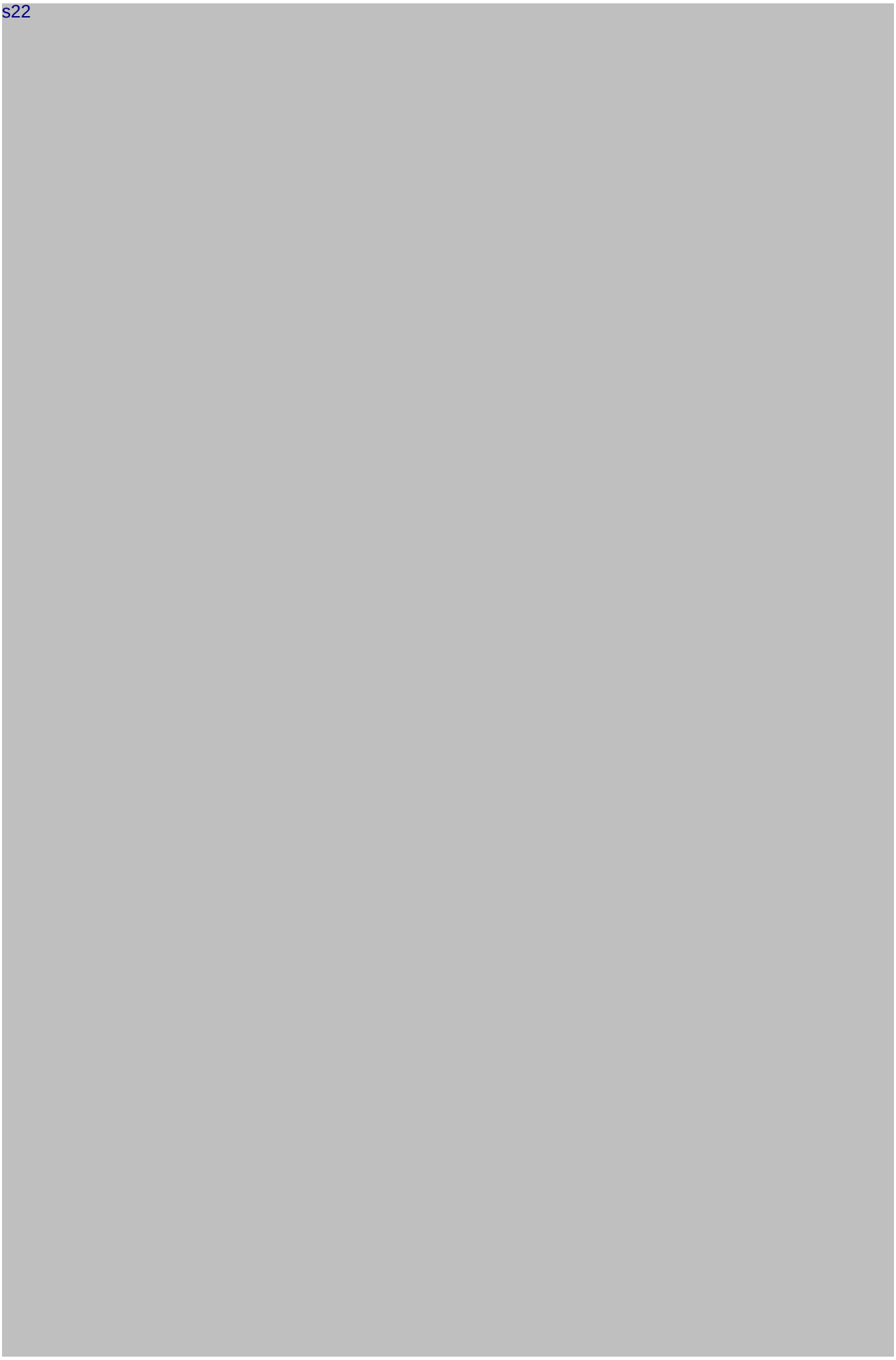

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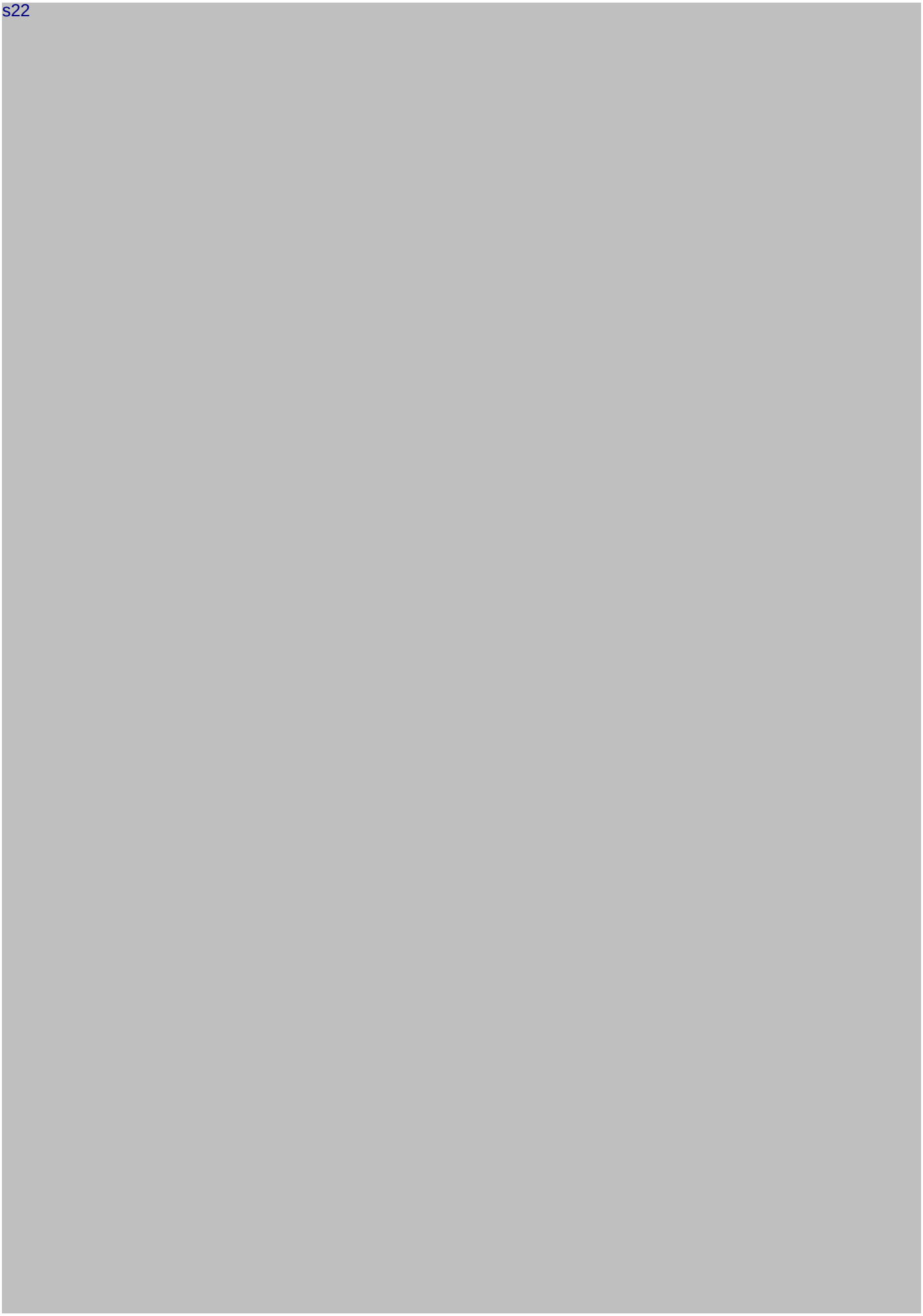

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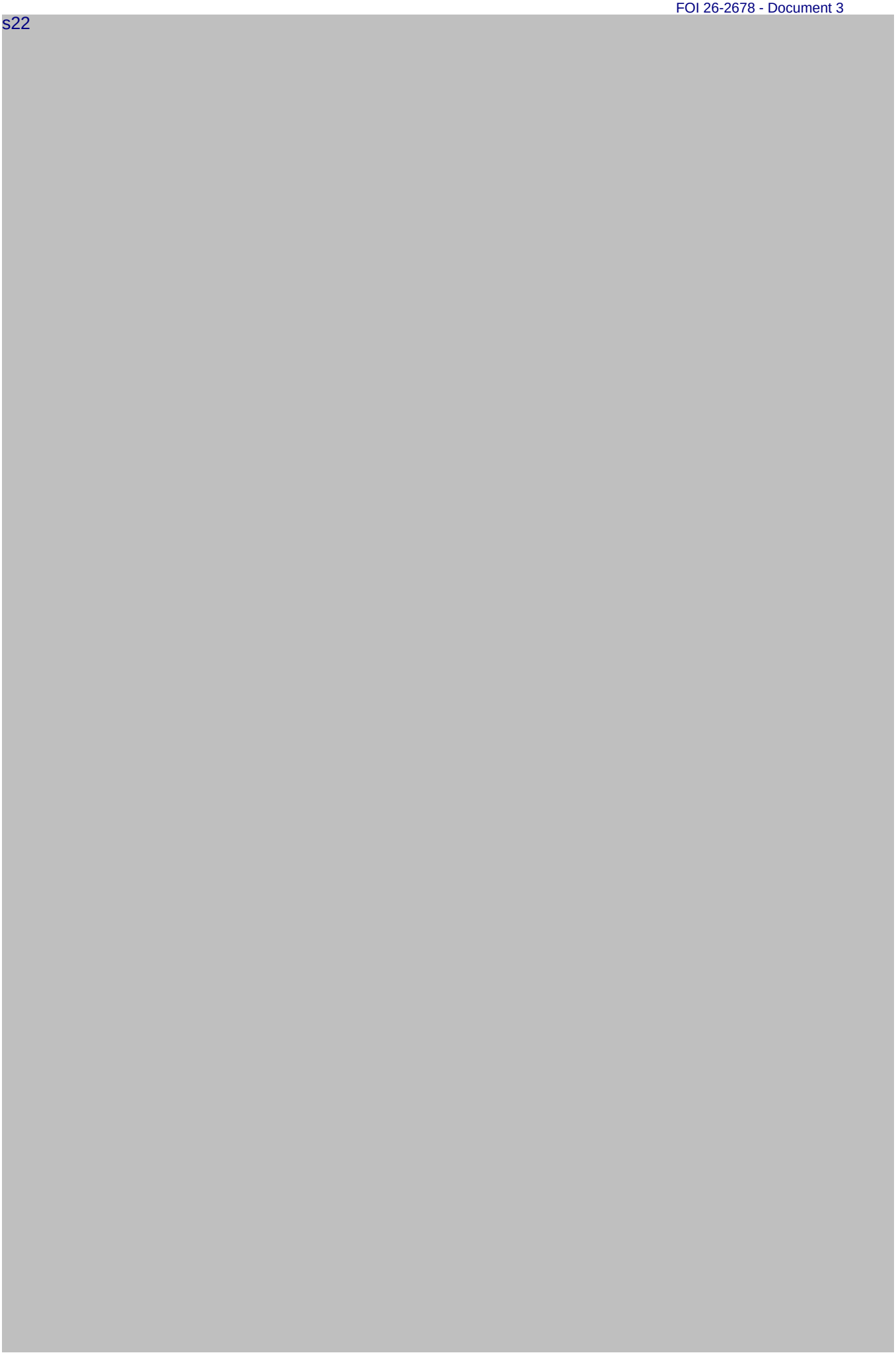

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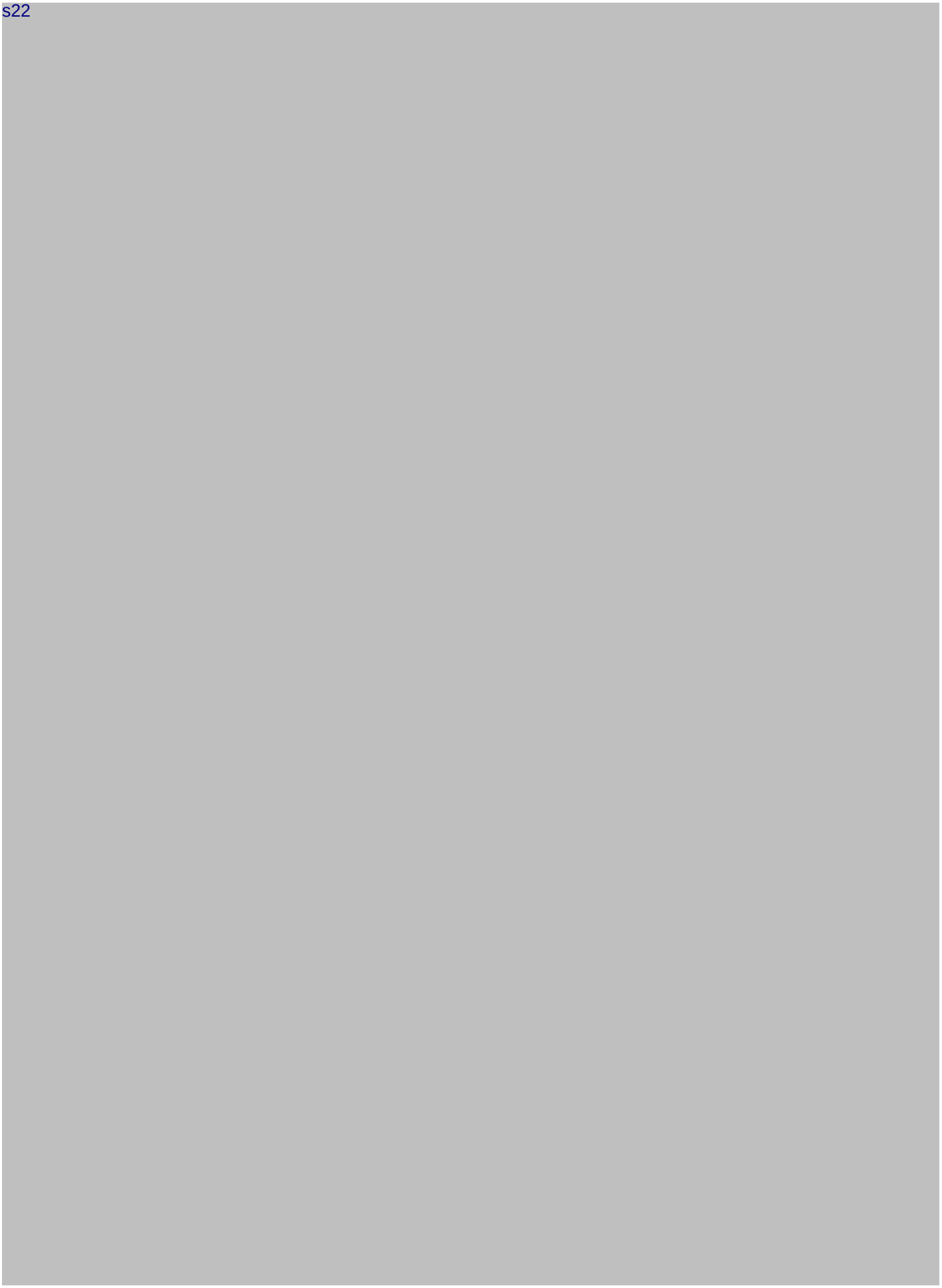

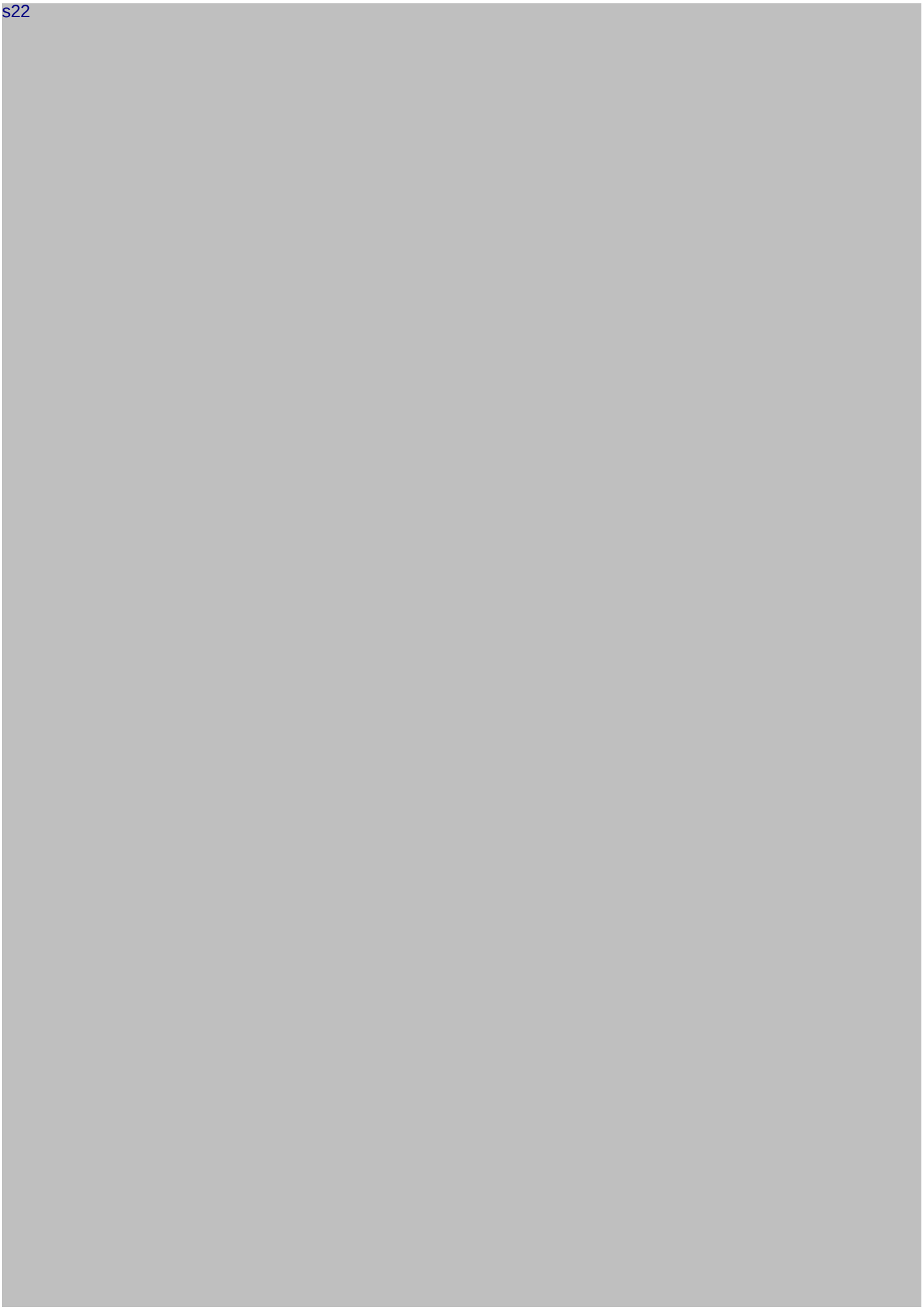
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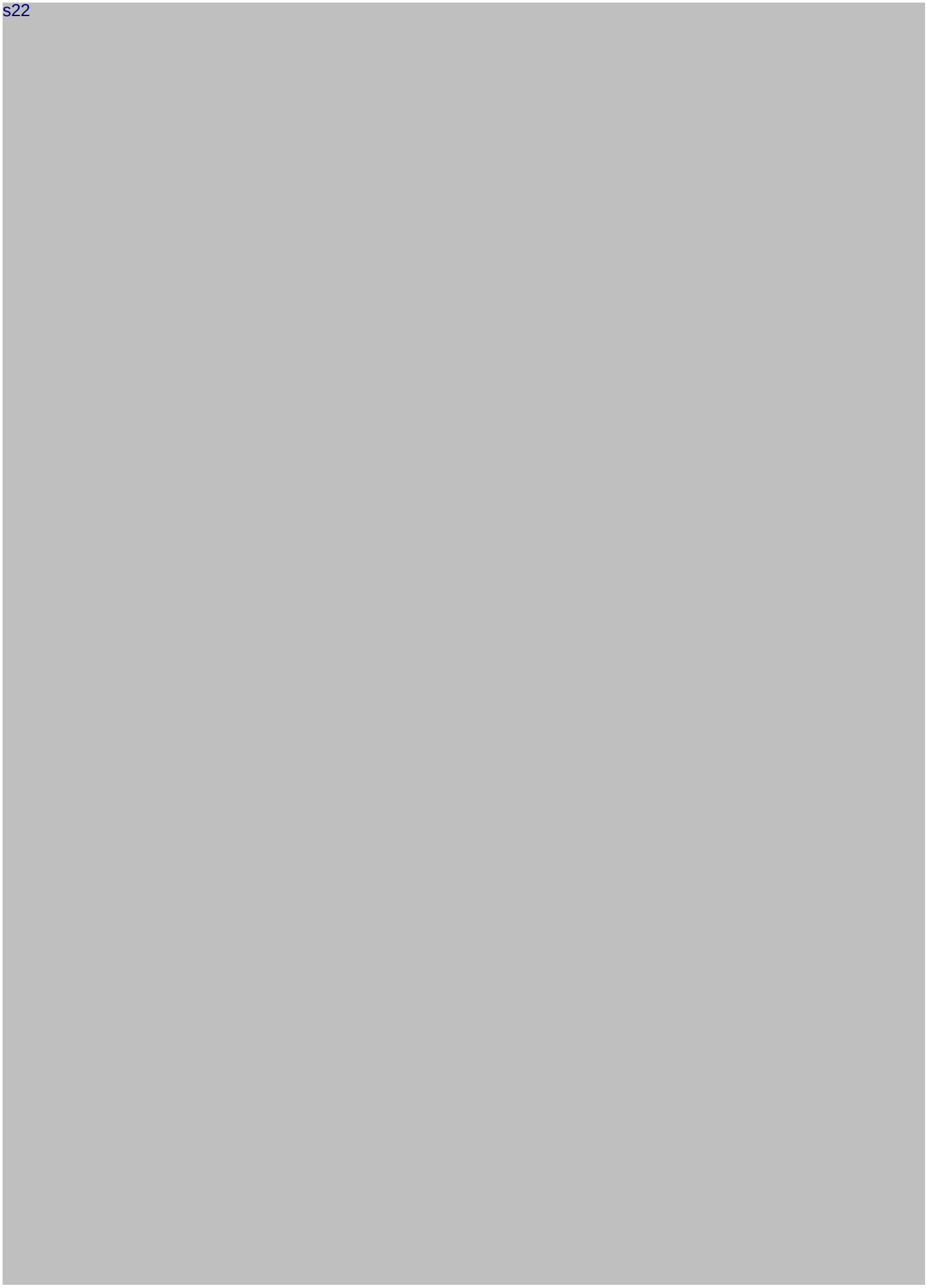

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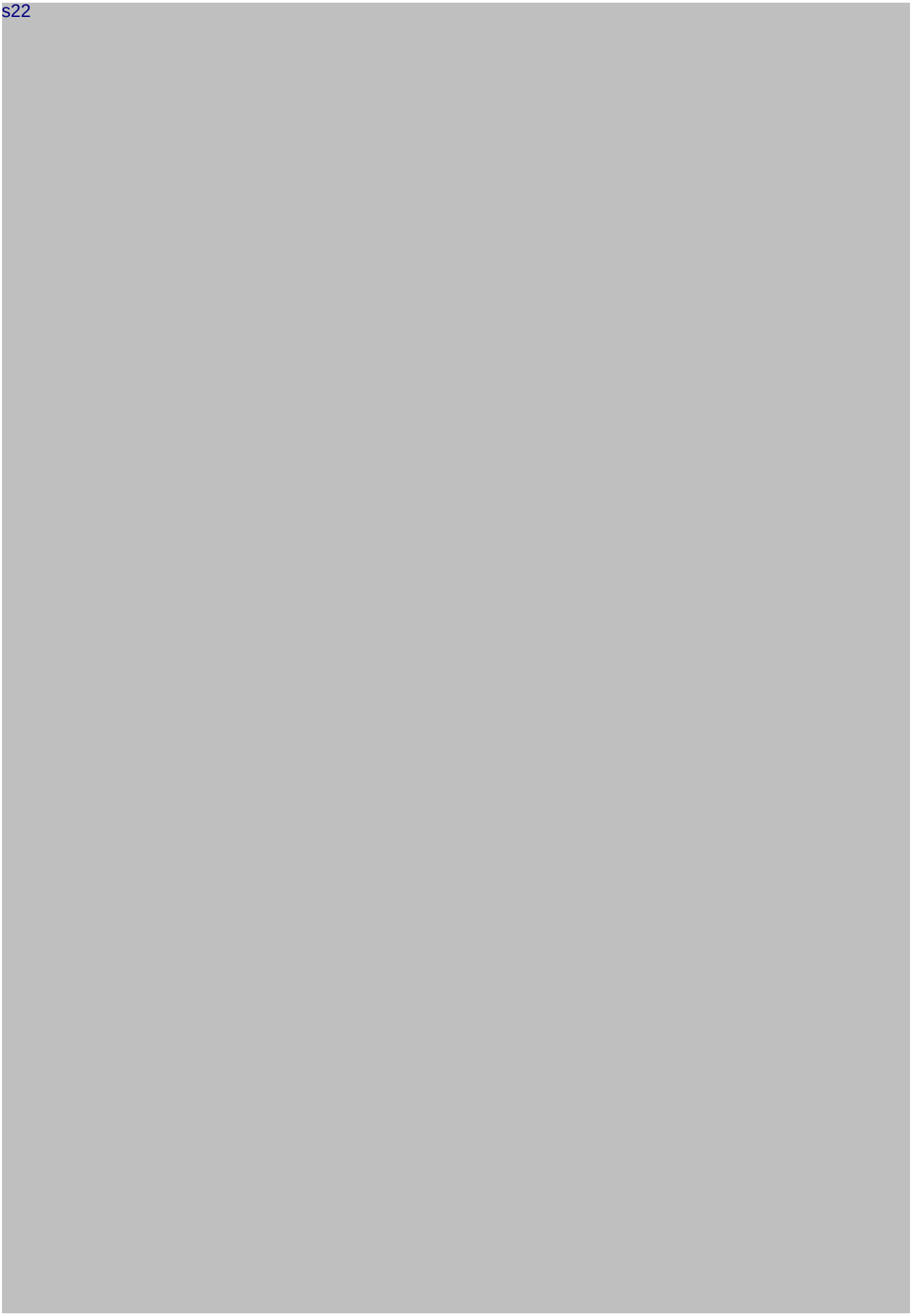

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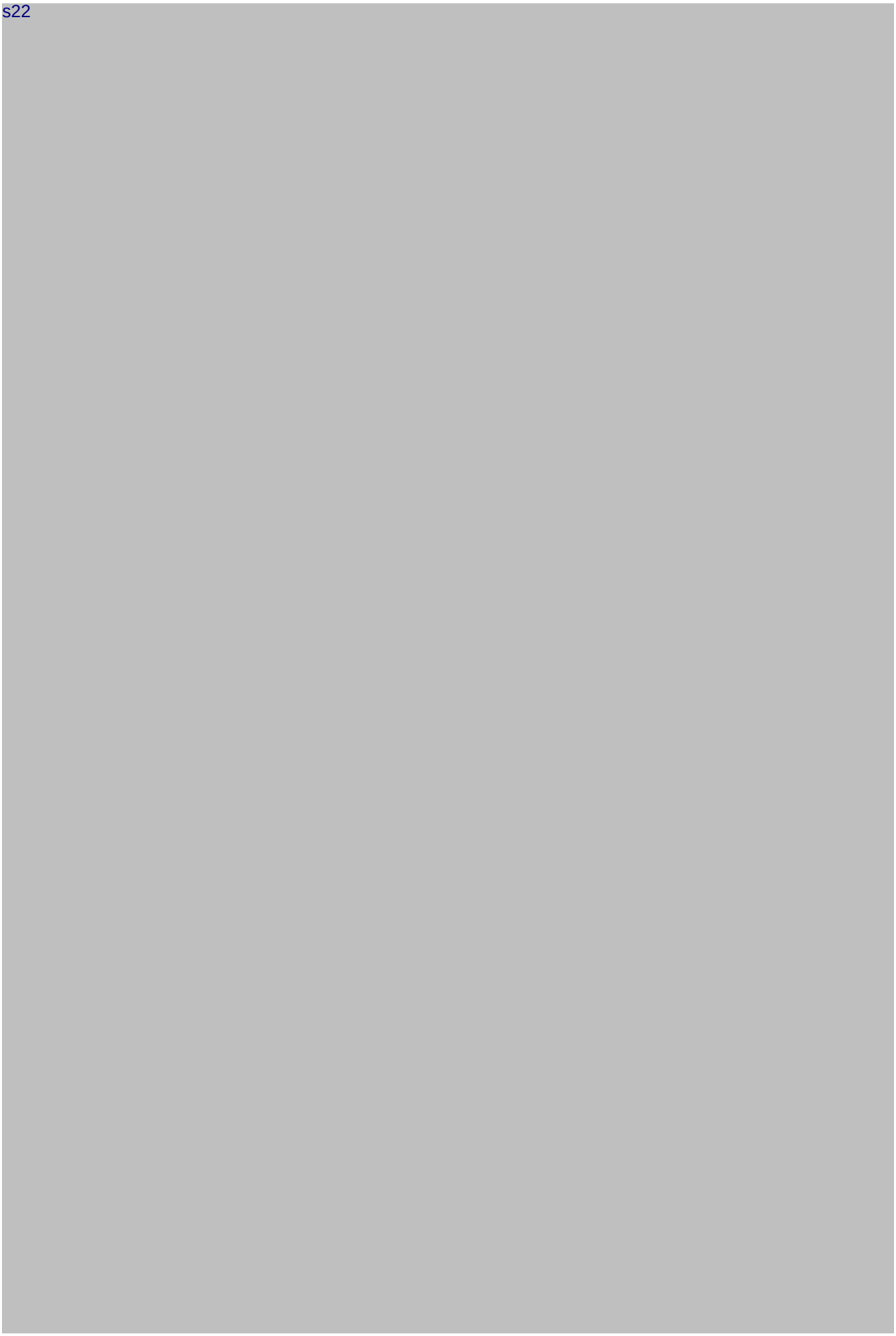

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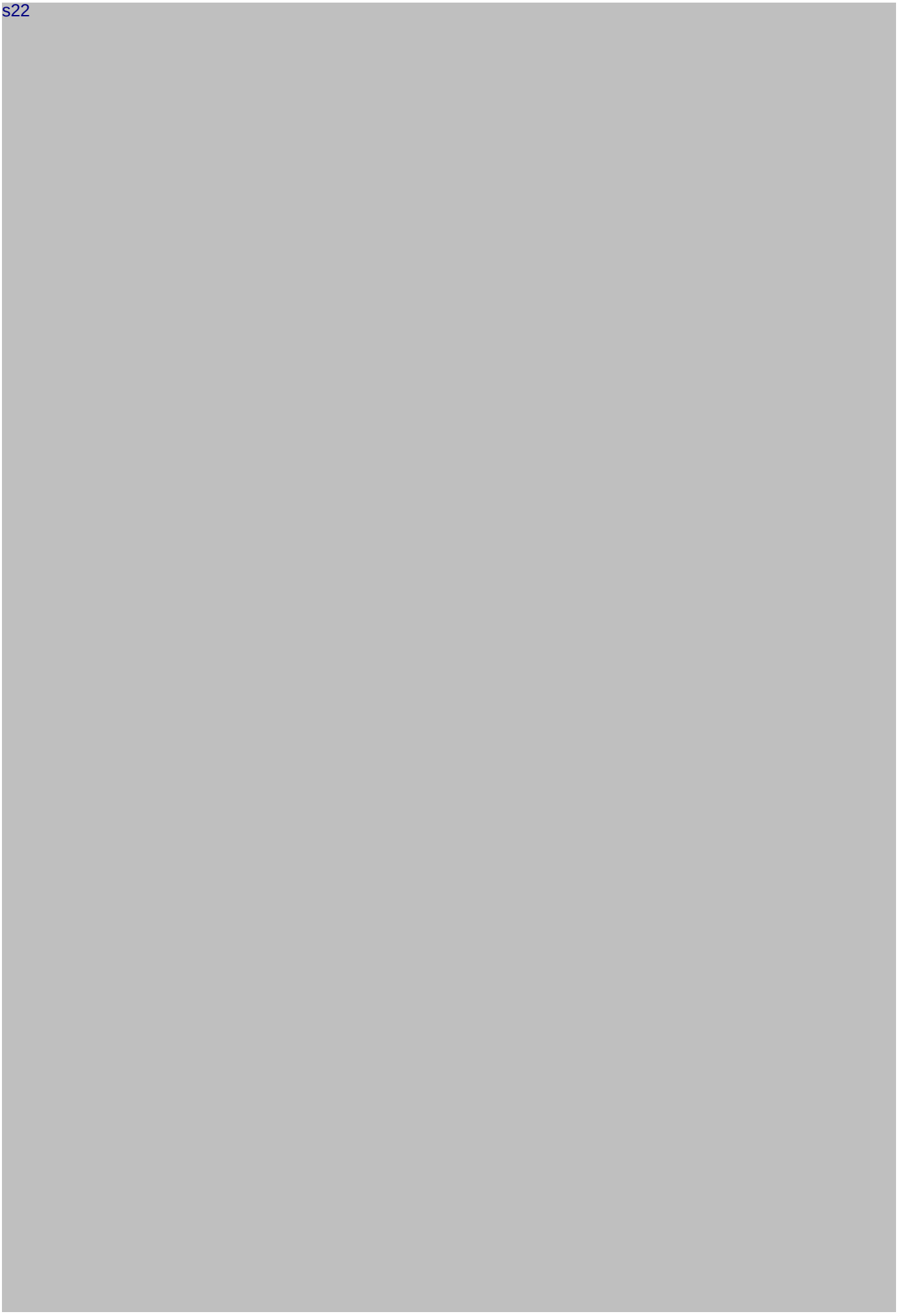

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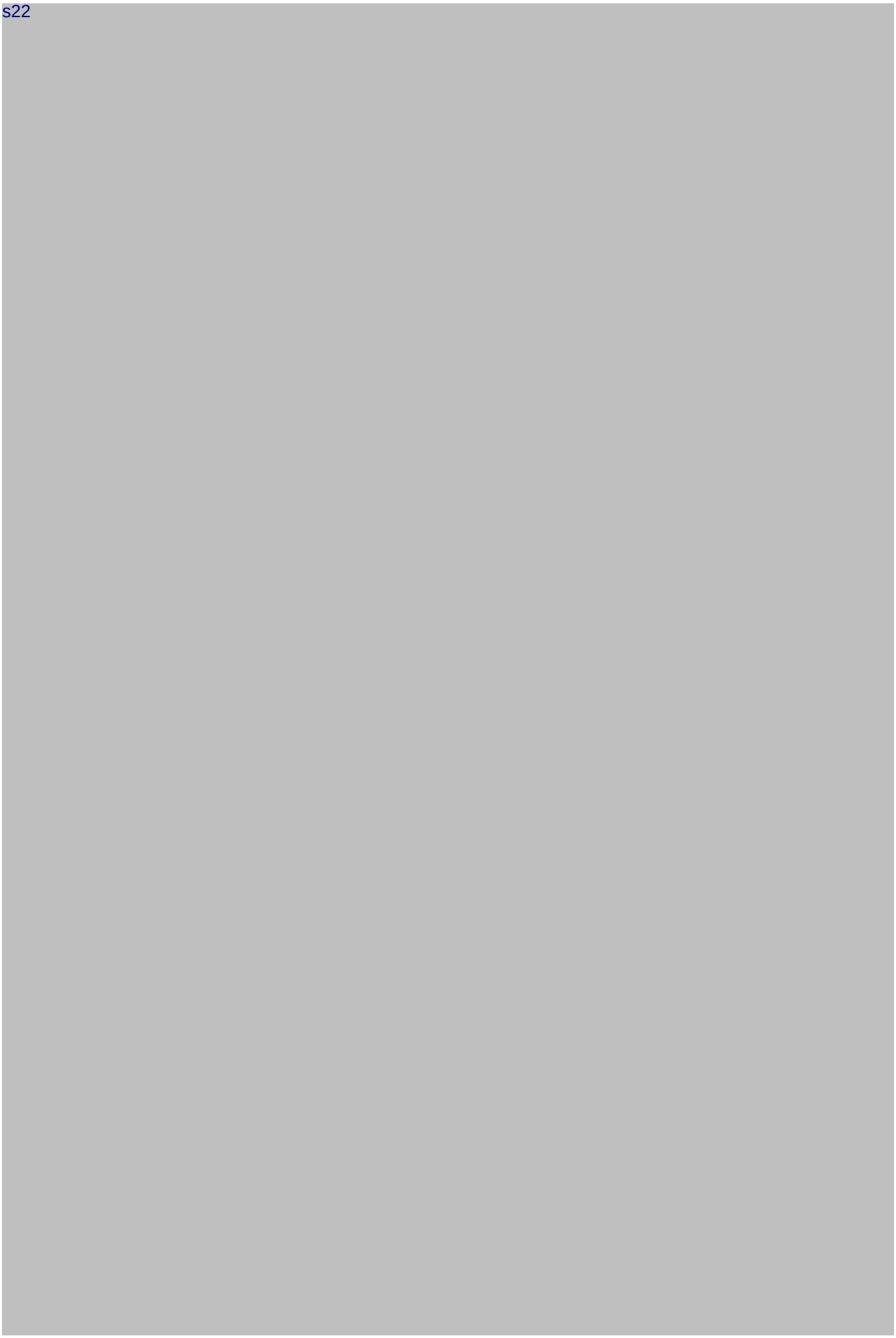

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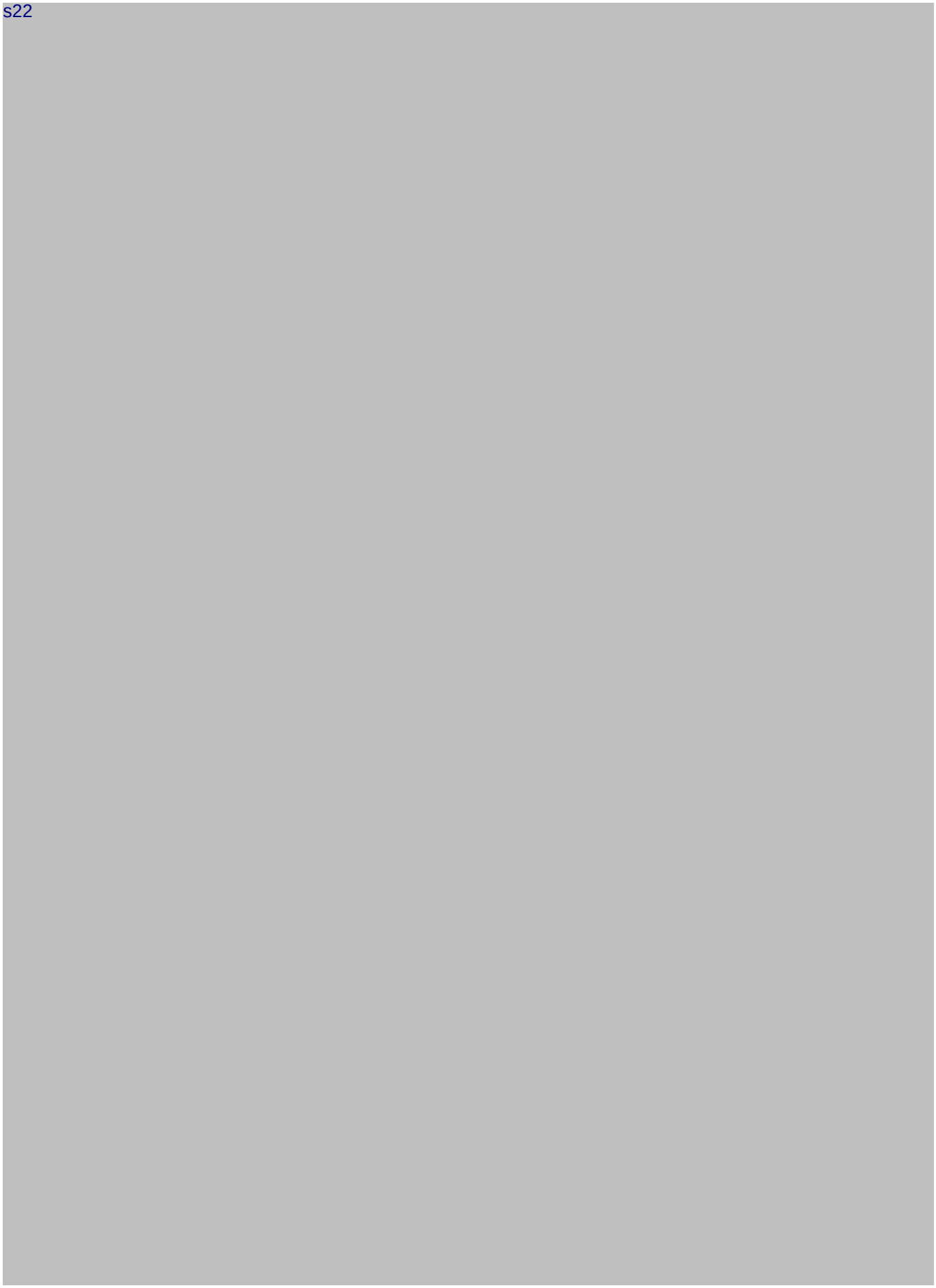


APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.

- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Time (AEST)	Activity	Staff involved
	PRE-INSPECTION CALL s22 *2023*	
10 – 11am	*Pre-inspection meeting* • Inspection logistics • Testing audio, video, screen sharing • Q&A	*TGA* s22 *Sponsor Staff* s22

Time (AEST)	Activity	Staff involved
	DAY 1 (onsite at sponsor address) s22 *2023*	
9:30 – 10.45am	*Opening meeting* • Introductions • Attendance • Scope • Confirmation of Inspection Plan	*TGA* s22
	Company Presentation Overview of the company and pharmacovigilance system (~30 mins)	*Sponsor Staff* s22
	Tour of office	
	Break	
11am – 1pm	**Case collection** • Spontaneous sources of data • Solicited sources of data	*TGA* s22 *Sponsor Staff* s22

Time (AEST)	Activity	Staff involved
1pm – 2pm	**Lunch/Break**	
2 – 4pm	**Maintenance of Reference Safety Information** • Overview of the management of variation requests (Sponsor and TGA initiated) • Process for the updating PI and CMIs following the identification of new safety information • Implementation of PIs and CMIs following approval • Package inserts and label	*TGA* s22 *Sponsor Staff* s22
4-5pm	• Spontaneous sources of data continued	*TGA* s22 *Sponsor Staff* s22
	DAY 2 s22 *2023*	
s22	**no inspection activities this day**	
	DAY 3 (remote) s22 *2023*	
9.30 – 11.30am	**Review of procedures for the management of:** • Case entry • Case management • Follow-up • Quality assurance **Expedited reporting of adverse drug reactions to the TGA**	*TGA* s22 *Sponsor Staff* s22
	Lunch/Break	
12.45 – 2.15pm	**Ongoing monitoring** **Management and reporting of significant safety issues to the TGA**	*TGA* s22

Time (AEST)	Activity	Staff involved
		s22 *Sponsor Staff* s22
2.30 – 2.45pm	**Discussion about maintenance of the FAQs**	**TGA** s22 **Sponsor Staff** s22
3.30-4pm	**Demo of** s47G(1)(a) **and** s47G(1)(a) **and maintenance of standard response letters**	**TGA** s22 **Sponsor Staff** s22
	DAY 4 (remote) s22 *2023*	
9-5pm	**Document reviews and ad-hoc interviews if required**	
11am – 12pm	**Role of the QPPVA and A-PVCP**	**TGA** s22 **Sponsor Staff** s22
	DAY 5 (remote)	

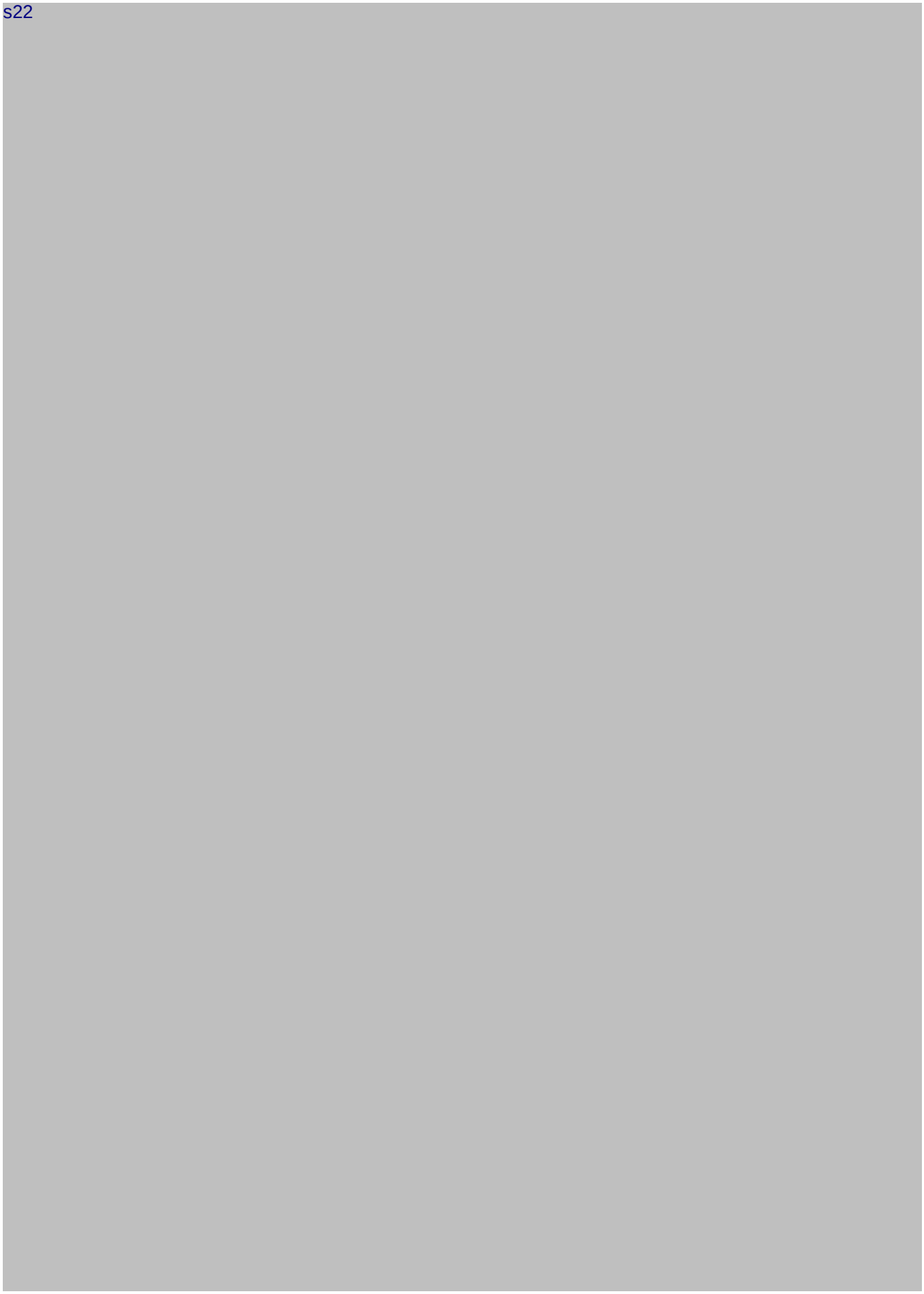
Time (AEST)	Activity	Staff involved
	s22 2023	
10am	**Cut-off for document delivery for the closing meeting**	-
3.30pm	*Closing meeting*	*TGA* s22 *Sponsor Staff* s22

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
APSS	Australian Pharmacovigilance Safety Summary
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
BTS	Black Triangle Scheme
CAPA	Corrective and Preventative Action
s22	
CMI	Consumer Medicine Information
COR	Comparable Overseas Regulator
CRM	Customer Relationship Management (system)
EMA	European Medicines Agency
ESI	Emerging Safety Issue
EURD	EU reference date
s22	
GSD	Global Safety Database
HCP	Health Care Professional
ICSR	Individual Case Safety Report
MedDRA	Medical Dictionary for Regulatory Activities
MI	Medical Information
MKR	Market Research (project)
NPP	Named Patient Program
PAC	Post-approval commitments
PI	Product Information
PQC	Product Quality Complaint
PRAC	Pharmacovigilance Risk Assessment Committee
PSP	Patient Support Program
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreement
PVIP	Pharmacovigilance Inspection Program
QC	Quality Control
QMS	Quality Management System
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
RASML	Required Advisory Statements for Medicine Labels
RMP	Risk Management Plan
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SOP	Standard Operating Procedure
SRR	Safety Related Request
SSI	Significant Safety Issue
TBS	TGA Business Services
TGA	Therapeutic Goods Administration

s22




s22

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22

RE: TGA Pharmacovigilance Inspection of s22

Please find attached the inspection report for the remote pharmacovigilance inspection of s22, conducted by the Therapeutic Goods Administration (TGA) on s22

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*. The purpose of the inspection was to assess compliance with the relevant pharmacovigilance legislation and guidelines and the conditions specified in the relevant approvals for registration or listing on the Australian Register of Therapeutic Goods (ARTG), and any subsequent variations.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021)
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as **APPENDIX I**).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Tracker.

For certain deficiencies, you may be requested to submit objective evidence of corrective or preventive actions after their completion dates.

Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed. In some circumstances, a re-inspection may be required to ensure completion of such activities.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22 2023

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor address:	s22
Main site contact:	s22
Inspection type:	Routine, system-related
Method of inspection:	Remote
Inspection scope:	To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines
Inspection date/s:	s22 2023
Inspector/s:	s22 (Lead), s22
Inspection finding summary:	0 Critical Deficiencies 5 Major Deficiencies s22
Date report issued to sponsor:	s22 2023
Reference:	E23-525806

Contents

s22

Introduction

s22 was selected for a routine inspection as part of the TGA's Pharmacovigilance Inspection Programme (PVIP); all acronyms used in this report are listed in **APPENDIX III**. The purpose of the inspection was to review compliance with currently applicable Australian pharmacovigilance (PV) regulations and guidelines. In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021) (*Pharmacovigilance Guidelines*)
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

Company background:

s22 is located in s22 and was established in s22 is a wholly owned subsidiary of s22 based in s22 is a global s22 company with presence in s22 countries, with the sponsor being the s22 affiliate established by s22. The sponsor employs over s22 employees across Australia and its portfolio of s22 individual entries on the Australian Register of Therapeutic Goods (ARTG) includes a range s22 medicines.

The sponsor pharmacovigilance (PV) system is divided into s22 categories, s22

s22 is the global owner of s22 sponsor products and is responsible for the s22 for those products. The PV responsibilities for s22 and the sponsor are outlined in the relevant Safety Data Exchange Agreements (SDEA) between s22 and the s22 For example, PV activities conducted by s22 include global literature search, signal detection and management, preparation of PSUR and RMP for those products and creation and maintenance of the global Company Core Data Sheets (CCDS). Safety information for s22 products is collected and recorded by the sponsor in the s47G(1)(a)

s47G(1)(a) partner companies are the owners of the global PV systems for s47G(1)(a) products. For these products, the sponsor operates their PV system in accordance with the responsibilities outlined in the relevant SDEA or Pharmacovigilance Agreement (PVA) with the respective s47G(1)(a) These agreements also outline responsibilities for the s47G(1)(a) to assist the sponsor to meet their PV obligations in Australia.

For products which are own solely by s22 the sponsor is responsible for all PV activities.

Safety information for sponsor products that are not s47G(1)(a) by s22 are recorded in s47G(1)(a)

The sponsor PV team consists of s47G(1)(a) personnel:

- s47G(1)(a) the Qualified Person Responsible for PV in Australia (QPPVA) and the Australian PV Contact Person (A-PVCP)

s47G(1)(a)

PV activities performed by this team include:

- PV training
- assessment and submission of Significant Safety Issues (SSI)
- case intake
- case follow up
- reconciliation of safety information
- oversight of PV activities performed by third party services providers.

PV activities contracted by the sponsor to s22 and s22 collectively include:

- Individual Case Safety Report (ICSR) processing
- notification of ICSR to the relevant partner company, where applicable
- local literature search
- global literature search, where applicable
- surveillance of regulatory intelligences from comparable overseas regulators
- signal detection and management, where applicable
- reporting of serious adverse reaction (SAR) to the TGA.

The sponsor s47G(1)(a) team is responsible for the submission of Periodic Safety Update Reports (PSUR), Risk Management Plans (RMP) and safety related requests (SRR) applications to the TGA for all sponsor products as required.

Within the sponsor's portfolio, s47G(1)(a) products required RMP and had an ongoing commitment for PSUR submissions to the TGA. s22 was included in the Black Triangle Scheme (BTS). At the time of the inspection, the sponsor did not have any patient support program ongoing in Australia. Several market research projects (MKR) had been conducted or were ongoing during the inspection period.

Brief report of the inspection activities undertaken

Scope of inspection

The inspection was conducted remotely via videoconference and included a review of both local and global PV systems. Company personnel from Australia s22 attended the inspection via videoconference.

The inspection was conducted through interviews and review of documents (including searches of PV, medical information (MI) and product quality complaint (PQC) databases). The PV topic areas reviewed during the inspection are highlighted in the Inspection Plan (attached as **APPENDIX II**) and included a review of:

- the collection, processing and reporting of spontaneous and solicited adverse reaction (AR) reports
- ongoing safety evaluation and the management of SSIs
- the management of reference safety information (RSI)
- the management of PV post-approval commitments (PAC)
- the quality management system (QMS)
- the role of A-PVCP and QPPVA.

Documents submitted prior to the inspection

The sponsor submitted an 'Australian Pharmacovigilance System Summary' (APSS) document on s22 s22 2023 to assist with inspection planning and preparation. Other specific documents including PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the sponsor prior to the inspection.

Conduct of the inspection

In general, the inspection was conducted in accordance with the Inspection Plan (attached as **APPENDIX II**).

Tabulated Summary of Inspection Deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing and reporting ARs and special situation reports received from spontaneous and solicited sources, were reviewed during the inspection. This included a review of all Australian reports received by the sponsor between s22 . When required, the narrative and source documentation for specific cases were analysed. Deficiencies related to the s22 and reporting of ARs are described s22 and Major Deficiency 3, respectively.
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of sponsor products were reviewed during the inspection. Deficiencies related to ongoing safety evaluation are described in Major Deficiency 2.
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the inspection. Deficiencies related to the management and reporting of SSIs are described in Major Deficiency 2.
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the inspection. Deficiencies related to the management of Australian RSI are described in Major Deficiency 1.
PAC	The procedure for managing PAC, including submission of PSURs, maintenance of RMP documents and implementing RMP commitments, was reviewed during the inspection. Deficiencies related to the management of PAC are described in Major Deficiency 5.
Role of the A-PVCP and QPPVA	During the inspection, the roles and responsibilities of the A-PVCP and QPPVA were reviewed. s22
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and standard operating procedures (SOPs), was reviewed during the inspection. Deficiencies related to the QMS are described Major Deficiency 4.

List of deficiencies identified during the inspection

Critical deficiencies

Nil Critical deficiencies were identified during the inspection.

Major deficiencies

1. Deficiencies in the Management of RSI

1.1. Delays in lodging the PI on the TGA website (after TGA approval)

In accordance with the Conditions of registration, sponsors **MUST** lodge any necessary updates to the PI within 2 weeks of the date of TGA approval.

A review of s47G(1) SRR submitted by the sponsor to the TGA revealed three examples of delayed lodgement of the updated PI on the TGA website, following the TGA approval. The delays ranged from 12 to 142 days. Details are provided in the table below.

Product	Variations to the PI	Date of TGA PI approval	Date of sponsor PI lodgement onto the TGA website	Approval to lodgement (days)	Delay (days)
s22				156	142
				37	23
				26	12

Deficiencies in the sponsor SOP for post-approval activities following PI approval may have contributed to the delays. This is further discussed in Major Deficiency 1.6.3

1.2. Delays in lodging Australian CMI (after TGA approval)

In accordance with the Conditions of registration, sponsors **MUST** lodge any necessary updates to the CMI to align with new PI changes within 2 weeks of the date of PI approval.

A review of SRR submissions to the TGA between the period s22 revealed two examples of delays in the lodgement of the updated CMI on the TGA website, following PI approval. The delays ranged from 2 to 210 days. Details are provided in the table below.

Product	Variations to the PI	Date of TGA PI approval	Date of sponsor CMI lodgement onto the TGA website	Approval to lodgement (days)	Delay (days)	Sponsor rationale
s22				16	2	The sponsor interpreted the two weeks' timeframe for the upload of the CMI as 14 working days.

s22	224	210	No rationale was provided on request.

Deficiencies in the sponsor SOP for post-approval activities following PI approval may have contributed to the delays. This is further discussed in Major Deficiency 1.6.3

1.3. Deficiencies in the maintenance of CMI following PI updates to ensure consistency

In accordance with the condition of registration, the sponsor **MUST** ensure that the CMI complies with the statutory requirements at all times, including consistency with the PI. If the related CMI document needs to be changed as a consequence of the change to the approved PI, it must be lodged with the TGA within 2 weeks of the date of the changed PI. In the case of changes relating to the safety or safe use of the product, more rapid change of the CMI may be warranted.

A review of the SRR submissions to the TGA between s22 revealed three CMIs where the content of the CMI was not updated, following the approval of variations to the PI. As of the first day of inspection, the CMIs were not updated. Details of the discrepancies between the CMI and the PI are described in table below.

Product	Summary of Warning statements in PI	Inspector identified differences between the PI and CMI	Date of sponsor revision of latest PI	Date of sponsor preparation of latest CMI	Sponsor's rationale
s22					The regulatory team reviewed the PI update and decided the warning cannot be translated for patient's use. There is no specific documentation detailing the review and the decision to not update the CMI.
					Rationale was requested but was not provided.
					Rationale was requested but was not provided.

The sponsor's rationale for not updating the s22 CMI was not considered acceptable. By not including the s22 in the CMI, the patient may not be aware of the s22 Since the prescriber may not be informed of the s22 Furthermore, the patient s22

Deficiencies in the sponsor SOP for post approval activities following PI approval may have contributed to the deficiencies in the maintenance of the CMI. This is further discussed in Major Deficiency 1.6.3

To ensure the safe use of medicines, it is necessary that CMI documents available to consumers are accurate and kept up to date.

1.4. Delays in updating Australian RSI (after sponsor identification)

In accordance with the *Pharmacovigilance Guidelines*, sponsors should ensure reference safety information (RSI) documents, including the Australian Product Information (PI) and Consumer Medicines Information (CMI), are kept up-to-date for safe use of the medicines by healthcare professionals and consumers. Sponsors should update RSI within a timely manner of identifying the need for change.

The TGA expects that any safety-related changes to update the Australian PI are submitted to the TGA within six months of a sponsor's identification of the need for change. This is irrespective of whether the product is currently marketed in Australia or whether the PI document is published on the TGA website.

A review of SRR submitted by the sponsor between s22 revealed two SRR that were submitted to the TGA more than six months after the date that s22 decided to update the PI. The two SRR were in relation to s22 and the duration between the s22 decision to update the PI to submission to the TGA were 276 days. The inspector noted the SRR relating to s22 and were submitted separately to the TGA on the same day. Details are presented in the table below.

Product	Safety-related variation	s22 decision date	Date of submission of PI update to TGA	Submission Number	Timeframe between s22 decision and submission of PI update to TGA (days)	Sponsor's rationale for the delay
s22					276	Sponsor received advice from s22 for the plan to update the CCDS and the final wording of additional text was received s22 .
					276	

The SDEA between s22 and the sponsor did not describe the timeframe from s22 decision to update the CCDS to the notification of update to CCDS to the sponsor. Deficiencies in the SDEA may have contributed this this deficiency and they are further discussed in Major Deficiency 5.2.

s47 which was effective at the time of these two SRR submissions, did not include a timeframe for the submission of SRR to the TGA from the sponsor decision date that a PI update was required. It is acknowledged that s47 did stipulate that SRR variations (that are not s22 alignment) are to be submitted to the TGA/s22 within six months of the date that any s22 personnel first decided that an update was required.

1.5. Deficiencies in providing accurate information on a sponsor website

In accordance with the *Pharmacovigilance Guidelines*, sponsors are responsible for the safe use of their medicine. Accurate and up to date reference safety information, such as contraindication and warning statements, is critical in ensuring current safety information is available to consumer and healthcare professionals.

Example 1)

Inconsistencies were identified between the safety information on a sponsor product website, compared to the current product PI.

On the s22 the sponsor's s22 was accessed to verify if the safety information on the website was consistent with the current CMI for s22 The s22 website was a publicly available website which provided information to consumers about s22 . Upon review of the website, inconsistencies were identified between the information on the website and the current s22

Details of the inconsistencies are provided in the table below.

Relevant section of the CMI	Content on the sponsor website	Content in the s22 CMI, Date of Preparation s22	Summary of key differences
s22			

s22

Providing inaccurate information relating to medicine on the website may lead to confusion and misuse of the medicine by the public.

Example 2)

On s22, the sponsor's website s22 was accessed to verify if the information relating to s22 on the website was accurate and aligned with the information on the product label.

One inaccuracy was identified in relation to the information on the website. The file name of the CMI was displayed as s22 which was confirmed by the sponsor to be incorrect during the inspection.

1.6. Deficiencies in sponsor written procedures for the management of RSI

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

1.6.1. Non-compliance with the SOP for the maintenance of Minimum PI

During the inspection, one example was identified where the sponsor's written procedure for the maintenance of Minimum PI, s47 , was not followed.

Following the TGA approval of the update to the s22 PI on s22 , the Minimum PI was not updated until s22 474 days later. However, this delay did not align with the process and timeframe specified in s47 , which stated that the s47G(1)(a) team will:

s47

The sponsor informed that at the time of the approval of the PI update, s22 was not a product with current or upcoming promotional activities which required material with Minimum PI, therefore it was determined that an update to the Minimum PI was not required at the time. In s22 an up-to-date Minimum PI was needed for anticipated commercial activities.

However, s47 did not specify that the time frame did not apply to products which are not currently promoted. Moreover, the procedure did not outline the circumstances where the Minimum PI will not be updated at the time of PI updates, or to document the rationale for the decision to not update the Minimum PI at the time of PI update.

The inspector noted that s47G(1)(a) outlined the procedure for post PI updates activities relating to Minimum PI and material. According to the SOP, updates to the PI would initiate a review of the Minimum PI against the PI updates for all products irrespective of the promotional status. However, s47 did not outline the need to document the rationale for the decision to not update a Minimum PI or materials, following PI update. This SOP is currently in training phase and has not been fully implemented.

1.6.2. Deficiency in the written procedure for the maintenance of promotional and non-promotional material

In accordance with the Conditions of registration, Minimum Product Information must accurately reflect the approved Product Information, including safety-related statements, but may be a paraphrase or précis of the approved Product Information

During the inspection, it was identified the sponsor's SOP for maintenance of promotional and non-promotional material, s47 , was incomplete.

s47 of the SOP provided high level descriptions of when promotional material should be renewed. s47 stated:

s47

However, it did not outline the procedure to follow after PI updates were approved by the TGA, to ensure the content of the material would be updated to align with the current PI, when required.

Whilst s47 outlined a procedure for the review of material after a TGA approved PI update, the need to document the rationale for the decision to update or not update materials following PI update was not described. Furthermore, s47 was not yet effective at the time of the inspection.

1.6.3. Deficiencies in the standard procedure for post-approval activities following PI approval

During the inspection, examples were identified where the sponsor's SOP for post approval activities following PI approval was incomplete.

Example 1)

The s47 did not stipulate the timeframe that should be followed for uploading the PI and CMI onto the TGA website.

s47

However, no timeframe was specified for the activities. During the inspection, the sponsor confirmed they did not have any formal written procedure in place for the monitoring and tracking of the above post-approval activities following the receipt of PI approval from the TGA, including the uploading of the PI and CMI via the TGA eBS portal.

Furthermore, the sponsor did not maintain a tracker for post-approval activities following TGA approval of the variations to the PI. The sponsor verbally confirmed there was no formal tracking for:

- upload of the updated PI and CMI to the TGA website
- assessment of the CMI following the approval of PI updates
- assessment of the impact of the PI updates on other reference safety information documents such as Minimum PI and related websites

In the absence of any formal tracking mechanism and the lack of timeframe requirement in the SOP, it was not clear how the sponsor would have adequate oversight to ensure that PI and CMI lodgement timelines could be consistently met, or that the sponsor personnel responsible for this task were appropriately trained on this task and the associated timeline for completion.

Example 2)

During the inspection, it was revealed that the sponsor did not consistently document the decision and the rationale to update, or not update, a CMI following receipt of a PI update approval from the TGA. Moreover, the sponsor SOP did not stipulate the timeframe required for the CMI review after the PI update approval.

s47

However, it did not outline the need to document the review of the CMI and the rationale for the decision to either update or not update the CMI following a PI update, therefore evidence of this review was not available unless the review resulted in an update. During the inspection, evidence for the review of the CMI associated with SRR submissions, including records for the rationale and decision to not update the CMI, was requested for a sample of products. Details of the products and the related submissions are described in the table below.

Products	Submissions number	Evidence of CMI review and decision to update or not update CMI available ?

		(Yes /No)
s22		No
		No
		No
		No
		No
		No

The sponsor confirmed there was no specific documentation of the review of the CMI nor the decision to update or not update the CMI. The inspector noted that the current s47G(1)(a) system allowed for the record of the decision to update or not update the CMI following a PI update. This function was not available prior to the update of the s47G(1)(a) system in s22

Without a specific timeline for the review of the CMI following receipt of the TGA approval of an updated PI, the sponsor SOP did not facilitate compliance with the mandatory timeline for CMI update and upload imposed by the TGA as a condition of registration.

2. Deficiencies in management of SSI

2.1. Late notification to the TGA of SSIs

In accordance with the *Pharmacovigilance Guidelines,* sponsors **MUST** report all significant safety issues related to their medicine to the TGA within 72 hours. We expect you to use your professional judgement in determining whether a safety issue is significant

A review of s22 SSIs submitted to the TGA in the period s22 revealed two delayed notifications of SSIs. The late SSI notifications concerned s22 which had a delay of 274 and two days respectively.

Product	Description of SSI	Date of first local awareness	Date of SSI assessment	Date of notification to the TGA	Time from local awareness to notification (days)	Sponsor's rationale for delay
s22					277	Initial assessment of issues was that the issue was not reportable and only an application to update the PI was required.
					5	No rationale provided upon request

2.2. Delayed communication of SSIs from global company and business partners to the sponsor

In accordance with the *Pharmacovigilance Guidelines*, the TGA recognise that safety information may be received and processed by your global counterparts before it is disseminated to the local affiliates in Australia for reporting to us. We expect you to have clearly documented internal procedures in place that ensure expedited communication of significant safety issues from the global personnel to your relevant Australian personnel for reporting (...) Substantial or

inappropriate delays between the global and Australian notification may be considered non-compliance with regulatory reporting timeframes.

A review of the SSIs notified to the TGA in the period from s22 revealed four SSIs, which were notified by either s22 or s47G(1)(a) to the sponsor within a timeframe ranging from 10 to 67 days, following the date of first global personnel awareness. The timeline for the notification from s22 or s47G(1)(a) represented non-compliance with regulatory reporting timeframes. Details of the examples are described in table below.

Product	High level description of SSI	Original Source	First s22 or s47G(1)(a) awareness date	First local sponsor awareness date	Time from global to local sponsor awareness (days)
s22					45
					67
					13
					10

s22

The inspector noted that the *SDEA between* s22 stipulated timeframes for exchange of safety issues, including verified or changing signals and any proposed changes in the labelling documents (including those due to class-effects) and specifically, a timeframe of s47G(1) for high impact safety findings (those signals that require immediate action), and no later than s47G(1)(a) for low impact safety findings after identification of the issue. Moreover, the following was stated:

s47G(1)(a)

However, these timelines were not followed for the s22 SSI described above.

The PVA between s22 and s22, which was effective at the time of the s22 SSI, did not stipulate a timeframe for the exchange of safety signals. The lack of timeframe outlined in the PVA for the exchange of identified or potential risks from s22 may have contributed to the delay in communication of the SSI to the sponsor.

The inspector acknowledged that the PVA between s22 and s22 were updated on s22 to include a timeframe for the exchange of signals. The agreement stated:

s47G(1)(a)

The inspector noted that the s47G(1)(a) stated:

s47G(1)(a)

However, this timeline was not followed for the s47G(1)(a) SSI described above.

2.3. Failure to perform cumulative review of safety information (signal detection)

In accordance with the *Pharmacovigilance Guidelines*, pharmacovigilance requires that you not only collect information on adverse reactions and significant safety issues, but that you also critically analyse and evaluate these to monitor the ongoing benefit-risk profile of your medicine. Safety monitoring activities should include a review of cumulative cases, in order to allow for comprehensive evaluation of the continuing safety and efficacy of the medicine.

Safety issues (or signals) may arise at any stage in the life cycle of a medicine, including the clinical development, manufacturing or in the post-market setting. You may become aware of safety issues from one or multiple sources which may suggest a new risk or a change in the nature of a known risk associated with your medicine. Safety monitoring activities should include a review of cumulative cases, in order to allow for a comprehensive review of potential safety issues. You should have a system in place for detecting and investigating such issues in a timely manner.

General safety information on your medicine including but not limited to ongoing monitoring activities should be retained indefinitely for the life of the medicine. We may also ask to review these records on request, or as part of the Pharmacovigilance Inspection Program.

During the inspection, it was revealed that the sponsor did not perform any cumulative review for s22 prior to the completion of the s47G(1)(a) report, dated s22 . The sponsor acquired sponsorship of s22 from s47G(1)(a) and it could not be verified if signal detection activities were performed by the sponsor for the product between s22 . This timeframe did not facilitate the timely detection and investigation of any potential safety issues for s22

Evidence of the sponsor's ongoing safety monitoring activities for s22 prior to s22 was requested and a s47G(1)(a) report, completed on s22 , for a review period s22 was provided. The frequency of the s47G(1)(a) report did not align with the frequency of s47G(1)(a) as recommended in s47 The sponsor informed that cumulative review was not performed, and no reports were prepared prior to s22 appointment as s47G(1)(a) on s22 and explained that,

s47G(1)(a)

Without sponsor records of signal detection activities, it was not possible to verify that this PV activity was performed for s22 between s22 , prior to the preparation of the s47G(1)(a) report dated s22

The inspector noted that s47 , which was effective at the time of the completion of the s22 report, did not outline the process of tracking signal management activities.

On s22 s47 was updated to s47 to include the use of the s47 s47 to plan and track signal management activities for a given year. The next s22 signal management activity was scheduled for s22 in the current s47 .

3. Deficiencies in reporting of SARs to the TGA

3.1. Late submission of SAR reports

In accordance with the *Pharmacovigilance Guidelines*, all serious Australian adverse reactions **MUST** be reported to the TGA within 15 days of receipt by the sponsor.

A review of initial and follow up SAR reports, submitted to the TGA between s22 revealed 13 (s47G(1)(a)) late submissions out of a total of s47G(1)(a) SAR reports to the TGA. The delays ranged from one to 33 days.

Further details of these late cases are provided in APPENDIX IV.

The inspector noted that CAPA plans were available for 12 out of the 13 late cases. A review of the 12 CAPA plans revealed:

- the root cause of 10 late cases related to delays in either a s22 or s22 providing the safety information or responding to a query relating to the safety information, outside of the timeline specified in the SDEA
- one case was late due to an IT issue with the sponsor email inbox
- one case was late due to the late reporting by sponsor personnel to the PV department.

The late case with no CAPA Plan was a spontaneous report regarding s47G(1)(a) which was also reported as a product quality complaint. As of time of inspection, s22 was investigating the non-compliance upon the sponsor's request.

3.2. Failure to submit SAR reports from literature

In accordance with the *Pharmacovigilance Guidelines*, you **MUST** report all serious adverse reaction cases occurring in Australia that are identified through screening the worldwide literature as soon as possible and no later than 15 calendar days from receipt.

A review of the source document (literature article) for case s47G(1)(a), deleted from the sponsor safety database on s47G(1)(a) revealed two valid SAR reports that were required to be recorded in the sponsor safety database and reported to the TGA by s47G(1)(a) Article, s47G(1)(a) was received to the sponsor on s47G(1)(a). Details of the cases are provided in APPENDIX V.

The sponsor provided the following rationale for the deletion of the case, "*The case was assessed for deletion as there was no adverse event.*" During the inspection, the sponsor clarified that the case causality between the suspected s22 products and the events were excluded, and the case was not identified as invalid and was deleted. No report associated with this article had been notified to the TGA by the sponsor at the time of the inspection.

Further details of sponsor management of this publication are discussed in s22

4. Deficiencies in the sponsor QMS

4.1. Deficiency in access to PV data

In accordance with the *Pharmacovigilance Guidelines*, you are responsible for the ARTG entries you hold and thus, you **MUST** ensure you meet your pharmacovigilance responsibilities whether you have contractual arrangements with other sponsors or external organisations.

Your pharmacovigilance system should meet any applicable record-keeping and reporting requirements. In terms of monitoring and collecting safety information, your pharmacovigilance system should allow you to identify and collect all information related to the safety of your medicine from all possible sources.

The pharmacovigilance data you collect, collate and electronically store MUST be available from a single access point within Australia.

> Source data—such as letters, emails, records of telephone calls that include details of an event and images of the source data—should be easily accessible. This allows initial and follow-up reports to be verified against the original data. This verification should be part of your quality control procedures.

During the inspection, it was identified that SDEAs with partner companies did not enable the sponsor to access all Australian PV data collected, collated and electronically stored from a single access point within Australia. It was also noted that case exchange from partners to the sponsor did not routinely include the provision of source documents. Therefore, source data for cases exchanged from the partner to the sponsor was not easily accessible.

A review of a sample of SDEAs between the sponsor and partner companies revealed that the partner did not exchange all Australian safety information with the sponsor. Whilst the sponsor informed that the s22 safety database was the 'single access point' as referenced in the *Pharmacovigilance Guidelines* for all sponsor products, the SDEAs did not facilitate the exchange of all Australian safety information to ensure that the sponsor could enter all PV data into their s22 safety database and therefore fulfil this access requirement. Furthermore it was noted that these partner companies were responsible for the global literature search for sponsor products and therefore would have a high likelihood to regularly identify non-serious and invalid Australian cases that were not exchanged with the sponsor to be available from a single access point within Australia. Details of the SDEAs reviewed in the sample are provided in the table in APPENDIX VI.

A comparison of a listing of valid cases from s22 against a listing of valid cases from the sponsor for the same period s22 revealed that numerous Australian non-serious cases, including special situation reports without an AE, were not included in the sponsors listing. Some examples of cases included; s47G(1)(a)

A listing from partner s22 of all serious, non-serious and invalid cases (ADRs and special situations) that occurred in Australia for the product s22 since the commencement date of the PVA to present was requested and reviewed against the sponsors safety database. The comparison revealed one example of a non-serious valid case, s22 , initially received by the s22 affiliate office, that was not exchanged with the sponsor. This case was initially received to the partner on s22 with follow up received on s22 . The case was not included in the sponsors listing of valid cases received to them between s22 The sponsor informed that this gap was previously identified which led to the amendment to the SDEA in s22 However, the sponsor did not confirm whether the case was subsequently entered into the sponsor safety database and the date of follow up with the partner regarding this case was not provided by the sponsor.

A listing from partner s22 of all serious, non-serious and invalid cases (ADRs and special situations) that occurred in Australia for the product s22 since the commencement date of the PVA to present was requested and reviewed against the sponsors safety database. Out of 16 cases, 13 cases were not exchanged with the sponsor to date. All of these cases were serious literature cases and therefore constituted potential missed SAR reports to the TGA given that the reporting responsibility lay with the sponsor according to the PVAs effective during the last two years. Details of these 13 cases are summarised in the table below.

s22 Case Id (MCN)	Case type	Date Received by s22 (Day 0)	Events (serious & non-serious; MedDRA PT*)
s22			

s22

*PT=Preferred term

The PVA included no timeline in which s22 were required to provide serious Australian cases to the sponsor. Specific timeframes and responsibilities for reporting of any case type were outlined only for the sponsor in relation to reporting safety information to s22 . Whilst it is acknowledged that the PVAs stated s47G (1)(a) the evidence showed that this provision was not sufficient to ensure compliance with the PVA nor Australian PV requirements for sponsors. Upon request for rationale for the lack of exchange of these cases the sponsor informed, "s47G(1)(a) ."

4.2. Deficiencies in the SDEA between the sponsor and s22

> In accordance with the *Pharmacovigilance Guidelines*, as a sponsor you are ultimately responsible for complying with Australian regulatory reporting requirements. You are responsible for the ARTG entries you hold and thus, you **MUST** ensure you meet your pharmacovigilance responsibilities whether you have contractual arrangements with other sponsors or external organisations. This also applies to overseas companies that belong to your parent company, and to other companies within or outside Australia with which you have commercial or contractual agreements—for example, vendors, partners and contract manufacturers.

The SDEA agreement between the sponsor and s22 did not sufficiently cover all relevant PV activities and the agreement did not fully enable the sponsor to comply with their PV responsibilities and demonstrated insufficient PV oversight from the sponsor.

Example 1)

Neither of the two SDEAs between the sponsor and s22 in force during the inspection review period s47G(1)(a) included any responsibility or timeframe for s22 to provide the sponsor with updates to the EU-RMP. In addition, no responsibility for the sponsor was included regarding maintenance of the RMP-Australian Specific Annex (ASA) and submission of updates to the TGA.

The approval letter (for s22 for an s22 for s22 imposed the specific condition of registration:

s22

Additionally, a comment in relation to the s22 RMP in the sponsor tracker, s47 however there was no responsibility regarding the conduct and assessment of effectiveness checks outlined for s22 in either SDEA.

Both SDEAs, included an "SDEA Checklist", a table which outlined responsibilities for each party for various aspects of the PV system. Whilst PSUR preparation and reporting to Regulatory Agency was included, the PAC of RMP was not addressed.

It is acknowledged that there were no updates to date to the content of the EU-RMP since the TGA approval, s22

Example 2)

Both SDEAs between the sponsor and s22 in force during the inspection review period s47G(1)(a) outlined the role and responsibilities for the management of CCDS. While the role and responsibility for the creation and maintenance of the CCDS and Company Core Safety Information (CCSI) lay with s22 the sponsor was responsible for the roll out of the CCSI into the local product information. However, both versions of the SDEA did not describe the responsibility and the timeframe relating to the notification of updates to CCDS from s22 to the sponsor. It was not clear if s22 was responsible for notifying the sponsor of CCDS updates and what timeframe was required for such notifications.

The inspector acknowledged that both SDEAs stipulated the timeframes for exchange of safety issues, including any proposed changes in the labelling documents (including those due to class-effects). The SDEAs described a time frame of s47G(1)(a) for high impact safety findings (those signals that require immediate action), and no later than s47G(1)(a) for low impact safety findings after identification of the issue which may impact the product. However, the evidence in Major Deficiency 1.4 showed that this provision was not sufficient to ensure CCDS updates would be notified to the sponsor in a timely manner

During the inspection, the sponsor confirmed that there was no specific timeline for s22 to send the updated CCDS pack to Australia.

4.3. Failure to implement agreement with PV responsibilities with MKR vendor

In accordance with the *Pharmacovigilance Guidelines*, sponsors need to be able to identify and collect all information related to the safety of their medicine from all possible sources to effectively monitor the medicine's safety. You are responsible for the ARTG entries you hold and thus, you **MUST** ensure you meet your pharmacovigilance responsibilities whether you have contractual arrangements with other sponsors or external organisations.

No contractual PV responsibilities were implemented with a vendor s22 contracted by the sponsor to conduct several MKR (at least s47G(1)(a)

During the inspection, two extensions s22 , to the s47G(1)(a) were reviewed in addition to the original Agreement. No PV responsibilities for either party were defined in the documents.

According to s47 at project initiation the s47G(1)(a) should notify the sponsor PV department via the s47G(1)(a) and approval of materials using PV Checklist and Risk Assessment.

The sponsor informed that a deviation was raised by the QPPVA (s47G(1)(a) with an initial identification date of s22 , during the initial TGA inspection request for information and following the sponsor discovery that s22 has conducted several MKR projects that did not undergo PV review or approval. The deviation was still open at the time of the inspection. It was found through sponsor investigation to date that the existing process in place since s22 whereby the PV team would send an email to the s47G(1)(a) to confirm a list of ongoing/planned MKR or marketing initiatives was ineffective.

A procedure, owned by s47G(1)(a) which outlined that PV review of relevant contracts must be completed before the agreement can be signed was in draft status at the time of the inspection. QPPVA review of this procedure occurred on s22

A deviation (s47G(1)(a) was raised by the QPPVA with an identification date of s22 , triggered by the TGA inspection preparation. The deviation outlined that on this date the QPPVA became aware that the s22 contract did not have a PV clause despite being "s47G(1)(a) " Sponsor investigations to date, conducted in association with the deviation, revealed that:

- The Master Services Agreement (MSA) template which included PV obligations had not been utilised at the time that the MSA with the vendor was implemented
- It could not be ascertained whether PV review of the agreement implemented with the vendor was conducted.

The agreement with s22 had not been updated in relation to PV at the time of the inspection.

4.4. Deficiencies in PV training

In accordance with the *Pharmacovigilance Guidelines*, sponsors should provide appropriate training to all staff engaged in pharmacovigilance activities or who might receive or process safety reports. Level of training should reflect the employee's roles and responsibilities. Pharmacovigilance training should be conducted at induction of employment, with an annual refresher at a minimum for all relevant staff as appropriate based on their roles and responsibilities.

4.4.1. Failure to provide PV training

During the inspection, three MKR projects were identified for which no evidence was provided of PV training for the staff conducting the activities. Details of the three projects are outlined in the table below.

MKR Project Title	Sponsor product	Vendor	Target recruitment	Start Date	Stop Date
s22					

s22

All PV training records for vendor, s22 staff, relevant to the five MKR they conducted for the sponsor between s22 were requested. A review revealed that one PV training record was available for one vendor employee, dated s22 . However, this vendor had initiated at least three sponsor MKR before this date, two of which were also completed prior to s22 s22

Without evidence of conduct of PV training for the vendor staff conducting these MKR, it was not possible to verify that safety information was collected from these activities. It was noted that the sponsor had not conducted any PV audit of this vendor and that the agreement with the vendor did, nor include any PV provisions, see Major Deficiency 4.3 for further discussion.

4.4.2. Delays in PV training

For nine out of s47G(1) personnel who commenced employment with the sponsor between s22 the first PV training was conducted more than one month after the commencement date of employment. Further details are outlined in the table below.

Name of personnel	Commencement date of employment	Role/job title	Date of first PV awareness training	Time from commencement date to first PV awareness training (days)
s22				

It was noted that the examples included healthcare professionals (HCP) facing roles such as s47G(1)(a) and s47G(1)(a)

It is recommended that initial PV awareness training is completed by personnel within their first month of employment to ensure timely identification and reporting of safety information. This timeline was also aligned with the sponsors SOP, s47 .

4.4.3. Deficiency in PV training materials

In accordance with the *Pharmacovigilance Guidelines*, sponsors should provide appropriate training to all staff engaged in pharmacovigilance activities or who might receive or process safety reports.

If you believe that there is a real patient involved (without any identifiers), it is considered sufficient for reporting.

All reports of adverse reactions, regardless of their validity, should be recorded in your pharmacovigilance system for use in ongoing safety analysis activities.

Ahead of the inspection, the sponsor provided three sets of PV training materials that had been used in the last 12 months as outlined in the table below. However, it was noted that the requirements for reporting safety information described in these slide decks did not align with the TGA PV requirements.

Training material title	Effective date	Audience
s47		

Specifically, the trainings did not outline the requirement to:

- report safety information in the absence of any patient identifiers if believed that a real patient was involved
- report safety information even if all four minimum criteria are no available (i.e. invalid reports).

Without training on these TGA PV requirements, it could not be verified that sponsor staff nor vendors collected and reported to PV all required safety information.

4.5. Deficiencies in PV procedural documents

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

Example 1)

A follow up form specifically developed and utilised to follow up an important potential risk did not have an associated document number, version number, effective date or author and therefore was not maintained as a controlled procedural document within the sponsors PV system.

The s22 was specified in the current s22 as a routine PV activity to be utilised in follow up of reported medication errors. The purpose of the form was to obtain relevant details to further characterise this potential risk as well as prompting the reporter for additional preventative steps which may reduce the risk of further errors.

The sponsor explained that the form was associated with the RMP therefore, the document control (date/author/version) is part of the RMP. However, inspector's review of RMP s47G(1)(a) and the current version of the RMP maintained by the sponsor s47G(1)(a) did not reveal the inclusion of the form. Instead, within RMP s47G(1)(a) the following information was included, "s22 " However, there was no s47G(1)(a) and s47G(1)(a) included with the RMP document. There was no mechanism therefore for document control of the s22

Example 2)

The s47G(1)(a) was an important PV tool utilised by PV staff in the conduct and oversight of reconciliation but this tracker was not referenced in the following relevant current SOPs:

- s47 , which outlined the process for reconciliation for internal functions and s22 and third-party service providers
- s47 which outlined the requirement for monthly oversight of reconciliation and assessment of compliance against the defined KPI.

4.6. Deficiencies in PV record keeping

In accordance with the *Pharmacovigilance Guidelines*, sponsors should retain literature review records and pharmacovigilance procedural documents indefinitely for the life of the medicine. We may also ask to review these records on request, or as part of the Pharmacovigilance Inspection Program.

The sponsor did not fulfil the record keeping recommendations related to literature review records and PV procedural documents and consequently the inspectors were unable to verify the compliance of the global literature review process for the sampled period.

Records of the global literature search results from s22 for four sponsor products (s22) were requested. However, upon review the records provided were not complete as they did not provide evidence of the reviews. For example, in weeks where the literature search retrieved "hits" for the sponsor product, N/A or only partially complete information was populated for a number of fields in the record (such as Literature Reference and the assessment fields) in place of information required to document the evidence of the search results and review.

The sponsor was unable to provide the procedural document followed by staff who performed these literature searches and reviews.

The sponsor informed that the searches were performed by a previously contracted vendor and no further records from them could be provided.

4.7. Deficiency in process for oversight of partner companies

In accordance with the *Pharmacovigilance Guidelines*, sponsors should make provisions for regular review for improvements to the system where required. We expect you to have an effective pharmacovigilance system. As a sponsor you are ultimately responsible for complying with Australian regulatory reporting requirements. You are responsible for the ARTG entries you hold and thus, you **MUST** ensure you meet your pharmacovigilance responsibilities whether you have contractual arrangements with other sponsors or external organisations. This also applies to overseas companies that belong to your parent company, and to other companies within or outside Australia with which you have

commercial or contractual agreements—for example, vendors, **partners** and contract manufacturers.

The QPPVA needs to have effective oversight of the entire pharmacovigilance system.

The sponsor did not have a quality assurance process for effective oversight of business partners who were responsible for significant PV activities as part of the PV system for those sponsor products, as outlined in the specific SDEA (refer to Major Deficiency 4.1 for details of examples of partner SDEAs).

The sponsor informed that sponsor procedure, s47 described the processes for PV audits. The purpose of this SOP was documented as,

s47

As part of the SOP, a s47, also referred to in the procedure as a s47, was one of the mechanisms to assess proposed vendors at the vendor selection stage.

The sponsor sent the s47 to partners for completion. Whilst partners, s22 and s22 did complete this questionnaire upon request on s22 respectively, s22 advised that they are not a vendor of s22 so the questionnaire would not be applicable.

In Australia, the sponsorship for s22 transferred from s22 to the sponsor on s22 and the first PV agreement was implemented on s22. Under the current PV agreement dated s22 were responsible for multiple PV activities including signal detection and assessment and global literature searching and management of Australian cases from the global literature search. However, the sponsor had never performed any audit of the partner to verify effectiveness of these processes in almost s22 years. It was noted that the PV agreement did include provision for both parties to audit each other.

Additionally, partner s22 did not complete the questionnaire upon request with the rationale (accepted by the sponsor) that the two PVAs in scope only recently became effective.

The evidence indicated that there was no sponsor process to audit and obtain oversight and assurance of the effectiveness of partner contractual PV responsibilities.

5. Deficiencies in the management of PAC

5.1. Late submission of a PSUR to the TGA

In accordance with the conditions of registration, sponsors **MUST** submit PSURs to the TGA in line with the timeframes and frequency specified in the approval letter.

During the inspection one late submission of a PSUR to the TGA was identified. A PSUR for s22 was submitted with a delay 24 days. Details of the submission are provided in the table below.

Product /ARTG No.	Period covered by PSUR	Data Lock Point (DLP) of PSUR	Date of PSUR preparation	Submission due date to the TGA	TGA submission date (actual)	Delay (days)
s22						24

The sponsor explained that s22 were responsible to produce and provide the PSUR to the sponsor as specified the SDEA, and the timeframe for provision of the report to the sponsor was no later than five calendar days before the target submission date. s22 provided the report to the sponsor on s47G(1)(a) Subsequently an email was sent by the sponsor to s22 colleagues, stating that PSUR submission to the TGA was not required on s22 . The sponsor further explained that due to technical issues, the PSUR report could not be validated in the TGA software despite numerous attempts.

A review of TGA records showed that the TGA contacted the sponsor on s22 regarding the overdue PSUR. The sponsor provided the pdf version of the PSUR and then the electronic Common Techical Document (eCTD) version of the PSUR on the same day by reply email.

There was no evidence of a deviation raised in the sponsors QMS regarding the late PSUR submission.

It was noted that the version of the sponsors SOP, s47

s47

The s47G(1)(a) was responsible to maintain the PSUR Schedule for assigned products. According to the s47G(1)(a) of the current s22 PSUR was added to the schedule s22 The delay in entry of s22 to the schedule may therefore have contributed to the delayed submission of the s22 in s22

5.2. Deficiencies in notifying the TGA of the commencement of supply

In accordance with the specific conditions of registration, the actual date of commencement of supply **MUST** be notified to the Head, Prescription Medicines Authorisation Branch, TGA. Should the sponsor decide not to proceed to supply, notification to this effect should be provided.

A review of evidence of notifications to the TGA of the commencement of supply for six sponsor products revealed a significant delay of more than one year between the first supply date and the date of notification to the TGA, for two products. Additionally, the notification of supply of s22 had not yet been conducted (in line with the condition of registration) more than one year three months after supply commenced. Details of the review of the six products are outlined in the table below.

Product / ARTG No.	Date of commencement of supply	Date of notification of supply to the Head, Prescription Medicines Authorisation Branch TGA	Time between date of commencement of supply and notification (days)	Sponsor rationale for the timeframe between date of commencement of supply and notification
s22				Oversight
				It was submitted to the RMP Coordinator, TGA instead
				Oversight

s22	Not applicable
	Not applicable
	Not applicable

Regarding s22, the sponsor informed that the date of first supply of s22 was alternatively notified by the sponsor to the TGA RMP Coordinator on s22 upon the TGA request for this information in association with the PSUR submission. However, this is not considered to fulfil the specific condition of registration which requires notification to the Prescription Medicines Authorisation Branch of the TGA.

It was confirmed in the inspection that the sponsor s47G(1)(a) team were responsible for the fulfilment of this specific condition of registration, however the team did not follow any SOP that included a timeline for completion of this task. In addition, there was no tracking of this commitment to ensure oversight that it was fulfilled in a timely way. The absence of a SOP or oversight mechanism may have accounted for the delay in notification of commencement of supply for s22 and s22 until the time of sponsor preparation for inspection.

Information relating to the supply of registered medicines in Australia is important for the TGA to prioritise PV monitoring, in the interest of public health.

5.3. Non-maintenance of the RMP

> In accordance with the TGA guidance, Risk management plans for medicines and biologicals, for products approved with an RMP as a condition of registration, the RMP should be maintained throughout the remainder of that product's lifecycle (even if we do not request an RMP for evaluation with applications for extensions of indication or other changes). You should update your risk management plan when new information becomes available regardless of whether your product is marketed. You should ensure that you always keep your RMP and ASA up to date for your own records and because we may request an updated RMP from you at any time.
>
> In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

During the inspection the current s22 RMP maintained by the sponsor was requested and reviewed. The review revealed that the content of the s22 had not been updated since s47G(1)(a) which was the version accepted by the TGA in the approval letter s47G(1)(a) This was despite numerous updates specific to the s47G(1)(a) and the associated additional risk minimisation activity.

Specifically, the Dear Healthcare Professional Communication (DHPC) letter was distributed in s22 According to the sponsors tracker, s47G(1)(a) effectiveness checks were s47G(1)(a) The first s22 PSUR was submitted to the TGA on s22 and summarised the effectiveness of the implemented agreed risk minimisation measures in section s47G(1)(a)

and in addition, outlined various additional activities since launch of the product in s22 to further mitigate the risk, that were not described RMP s47G(1)(a) as follows:

s22

At the time of the inspection there was no effective SOP that outlined sponsor responsibility and timelines for the ongoing review, maintenance, and assessment for any required update for submission to the TGA in relation to RMPs agreed as a condition of registration. The current version of sponsor s47 did not outline the requirement to maintain and update RMPs, identify what may trigger the need to review and update the RMP, nor specify the requirement and timeline in which to submit important updates to the TGA.

5.4. Deficiency in the oversight of the management of PAC

> The QPPVA needs to (...) have effective oversight of the entire pharmacovigilance system. The Qualified person responsible for pharmacovigilance in Australia (QPPVA) should ensure that the sponsor (...) complies with the legal pharmacovigilance requirements.

The sponsor did not maintain a tracker of all PAC to the TGA for oversight purposes. Although the sponsor tracked some PAC, such as the submission of PSUR and RMP, no evidence of tracking was provided for other commitments, for example:

- TGA notification of the commencement of supply
- inclusion period in the BTS
- or other specific conditions imposed in the approval by the s47G(1)(a) such for example, s22

Without a comprehensive tracking system, it was not possible to verify the sponsor oversight of compliance with all PAC relevant to the sponsors PV system, imposed by the TGA for sponsor products.

5.5. Deficiency in written processes regarding RMP Risk Minimisation activities

> In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

Despite a period of almost one year between the approval of s22 (which included agreement to an additional risk minimisation measure of a DHPC letter) and supply of s22, the sponsor did not develop a SOP during this time and before commercial supply of the product, to describe the roles, responsibilities, requirements and timelines for the planning, management and assessment of effectiveness of additional risk minimisation measures.

The s22 Australian RMP s22 was submitted to the TGA on s22 and agreed with the TGA as part of approval for submission s47G(1)(a) granted on s22 . This RMP outlined an additional risk minimisation measure of,

s22

Current sponsor SOP, s47 which was also adopted by the TGA. However, at the time of the sponsor planning, distributing and assessment of the s22 DHPC letter in s22 and s22, this SOP did not include any written process associated with these activities. It was noted that the SOP was updated in s22 after sponsor awareness of the s22 additional risk minimisation measure, however this update concerned only, s47

The sponsor rationale for a lack of procedure was sought and the sponsor explained,
s22

It was acknowledged that the sponsor provided evidence that the effectiveness of the delivery method of the s22 DHPC letter was assessed. In addition, the sponsor had subsequently identified the need to introduce formal written processes for this area of their PV system including:

- the need to revise s47 to address effectiveness checks for RMP activities (the SOP update was in draft status at the time of the inspection)
- the need for a formalised process specific to DHCP letters including the development, distribution and assessment of DHCP Letters s47 was not yet effective at the time of the inspection).

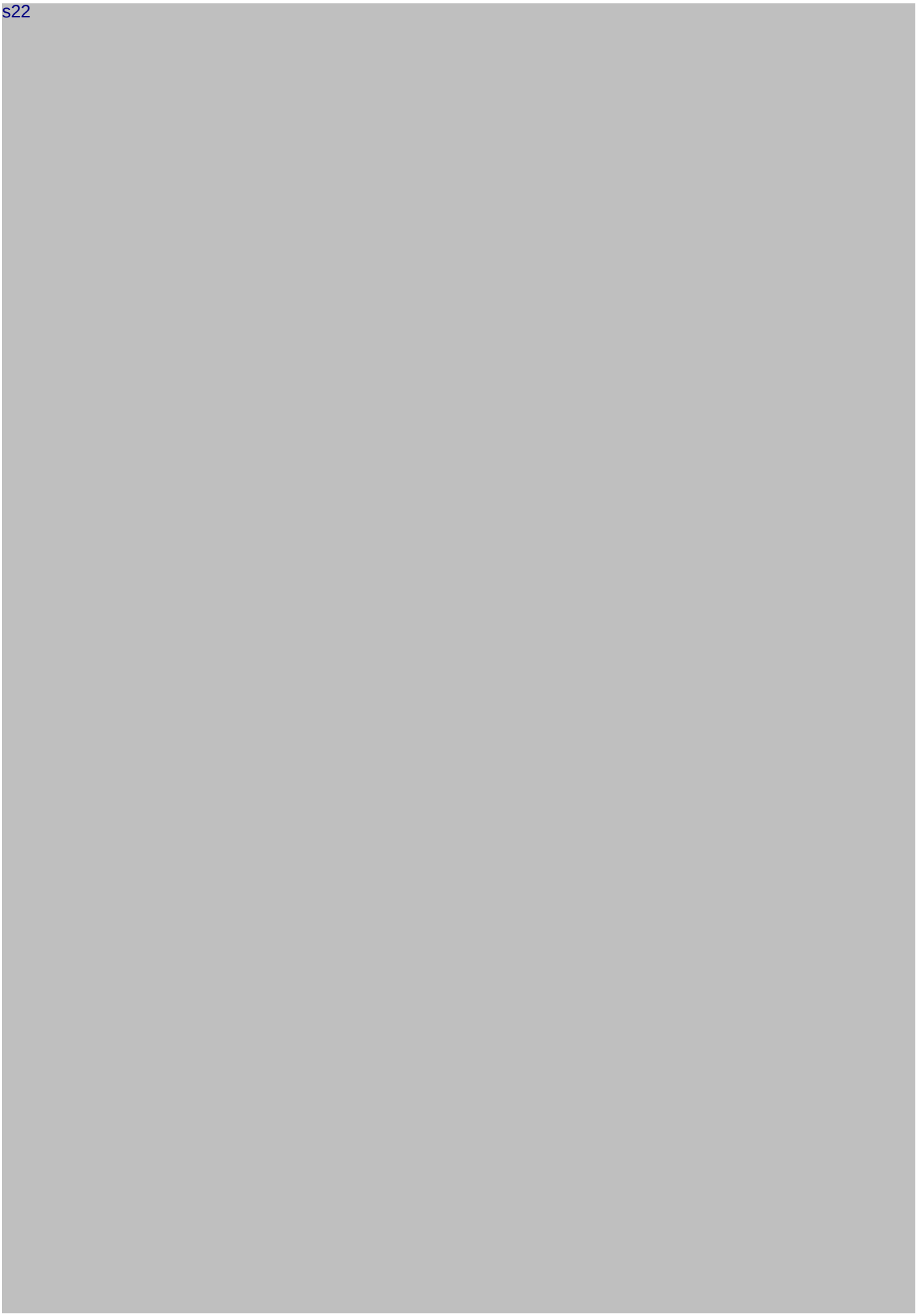
5.6. Inclusion of incorrect/out-dated information the RMP-ASA submitted to the TGA

s47G(1)(a) of the s22 Australian RMP submitted and agreed with the TGA as part of approval for submission s47G(1)(a) included incorrect information regarding the QPPV and the QPPV oversight declaration.

The s22 Australian RMP was updated from s47G(1)(a) in s22 and submitted to the TGA in s22. The date of final sign off of s47G(1)(a) was recorded in the RMP as s22 s22. The signatory was the indicated to be the QPPV and the name s22 was recorded. Furthermore, the RMP included a QPPV oversight declaration, "*The content of this RMP has been reviewed and approved by the sponsor's QPPV. The electronic signature is available on file.*" However, at the time of sign-off of s47G(1)(a) of this RMP, s22 was not the sponsor QPPV and he had ceased employment by the sponsor in s22 therefore it was not possible that s22 had reviewed and approved the entire content of s47G(1)(a) of the RMP.

The sponsor explained that s47G(1)(a) included minor changes compared to s47G(1)(a) and that,
s22

The sponsor rationale did not justify the inclusion of a person not employed as the QPPV, as the signatory and author of the QPPV oversight declaration, for a new version of the RMP. It was also noted that at the time of sign-off of s47G(1)(a) of this RMP, a Deputy QPPVA was appointed who was a long-term employee of the sponsor.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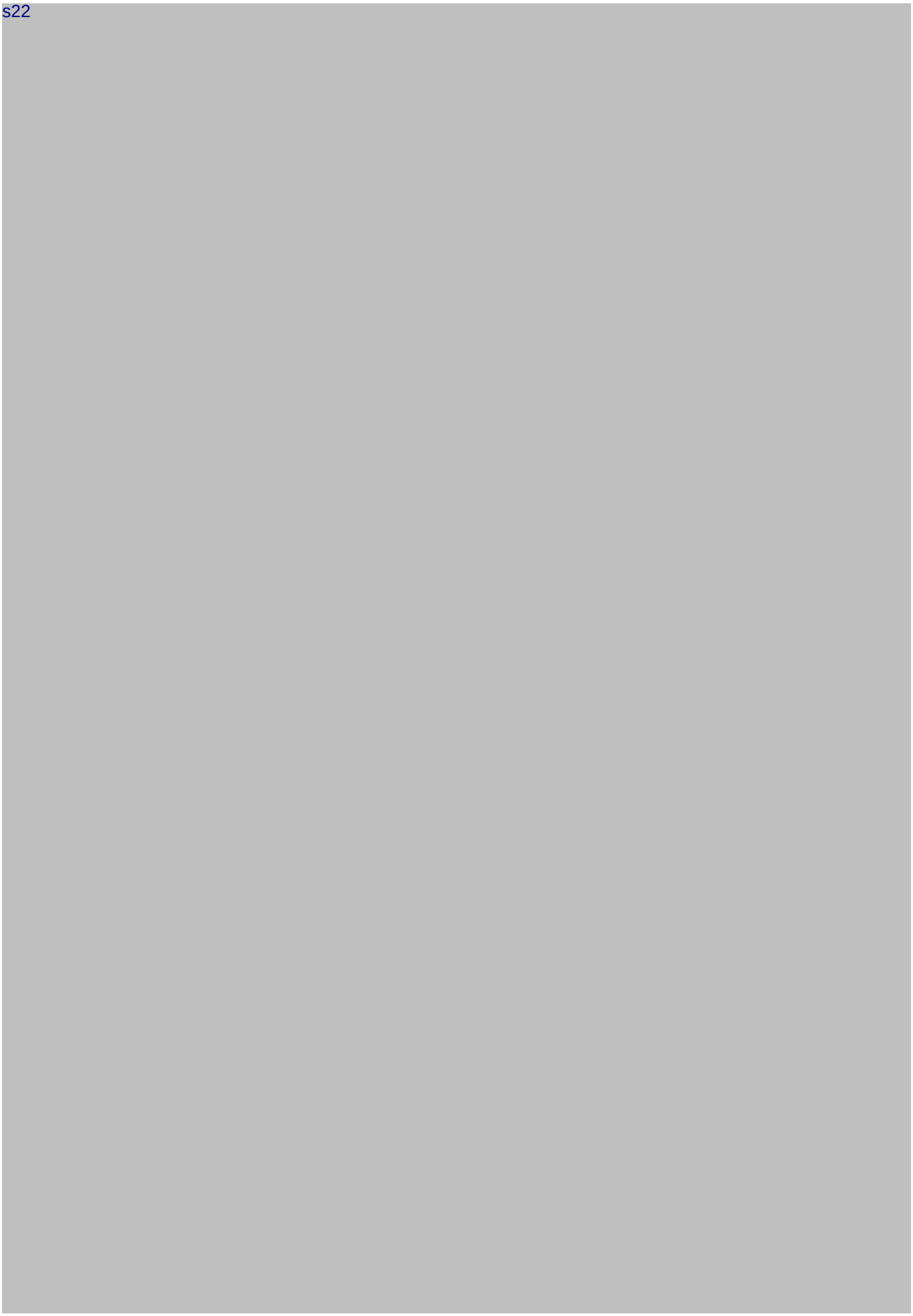

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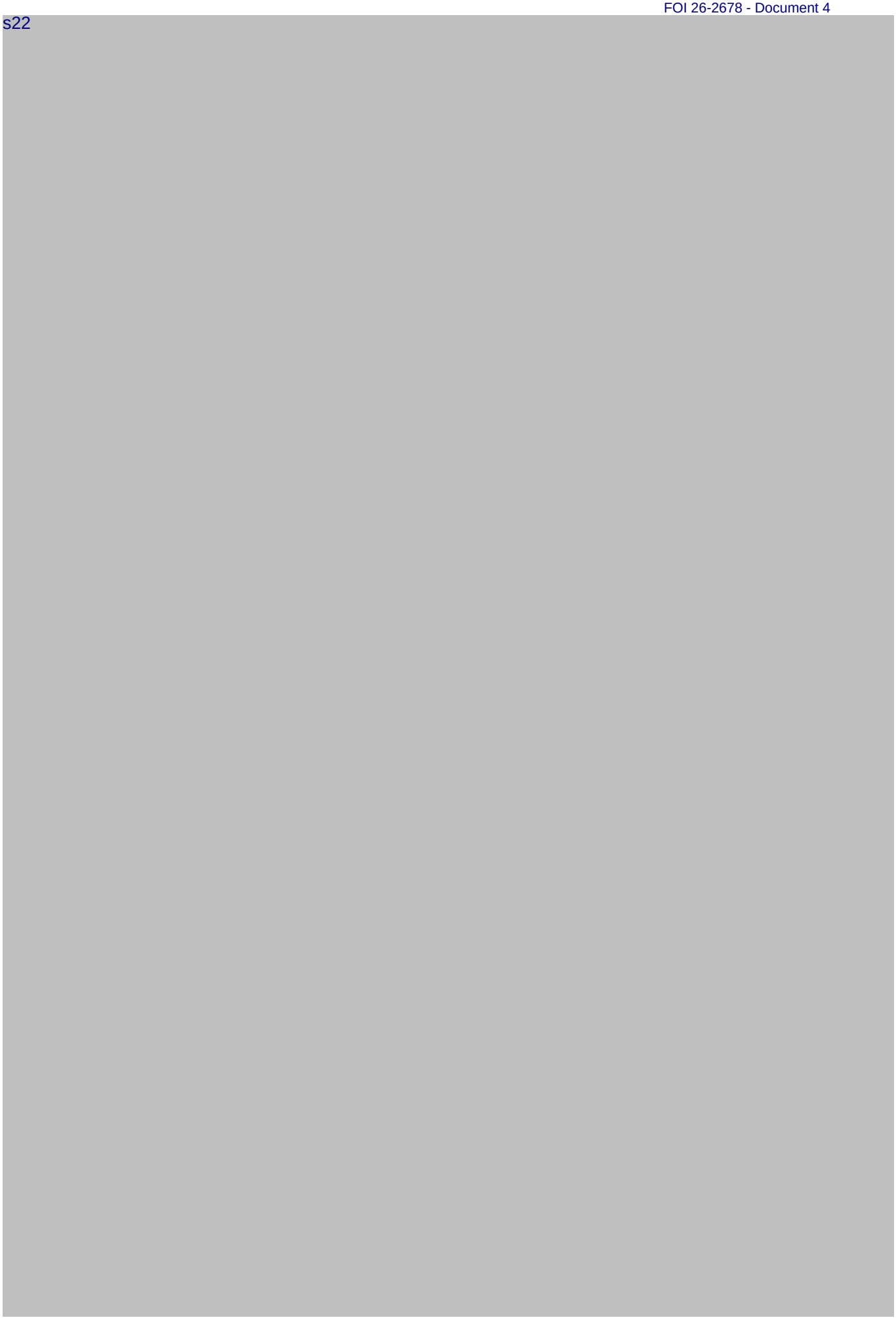

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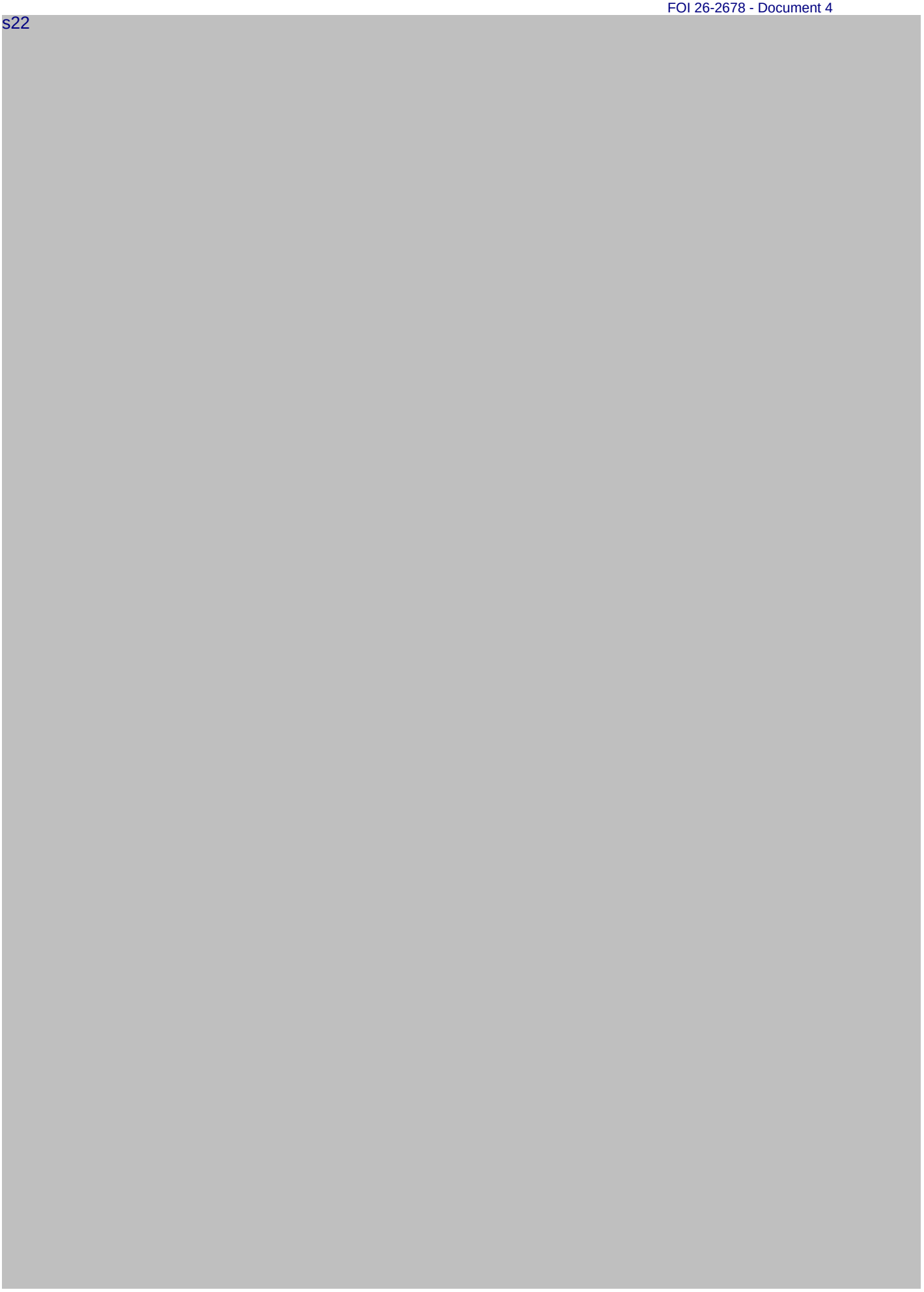

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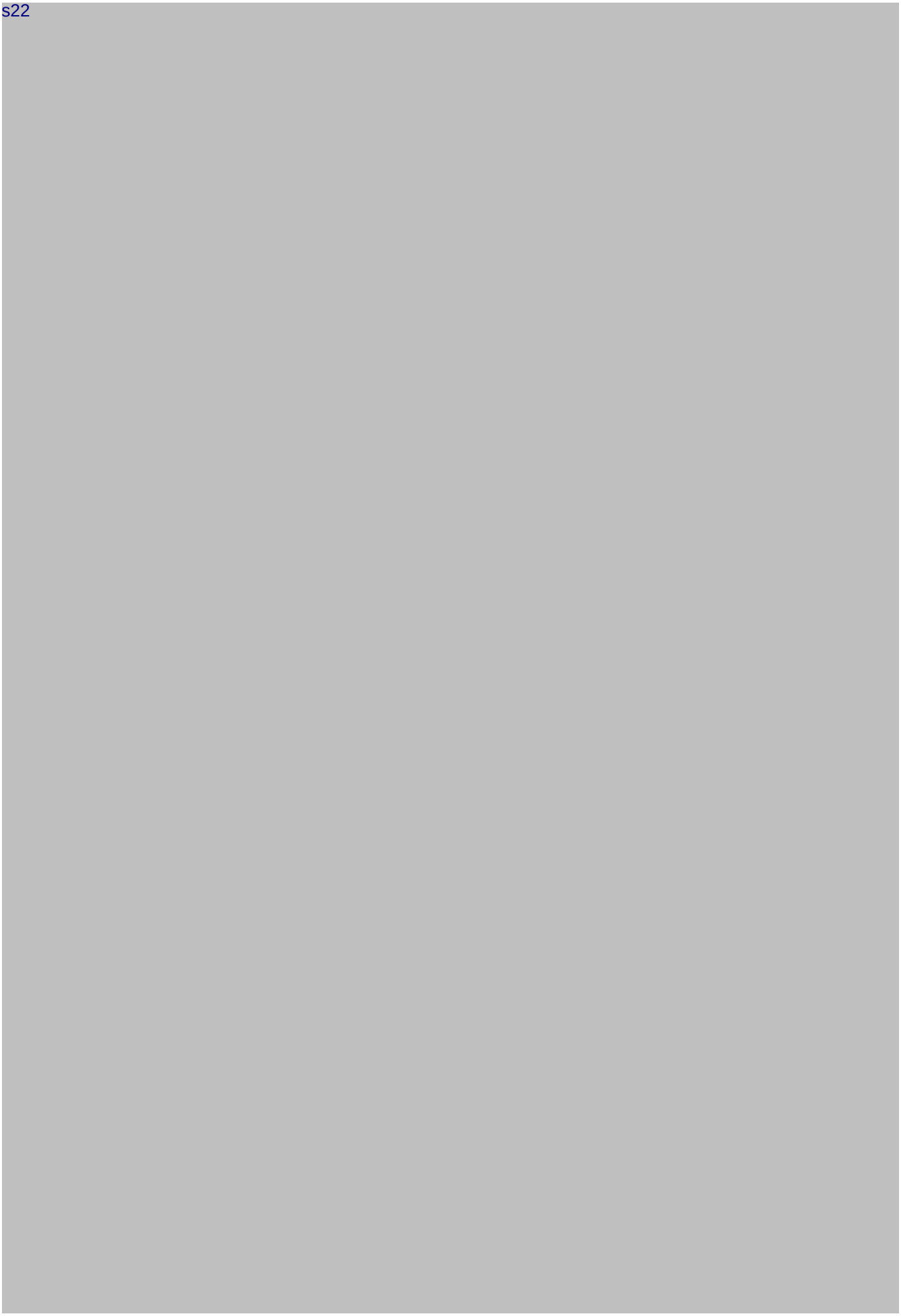

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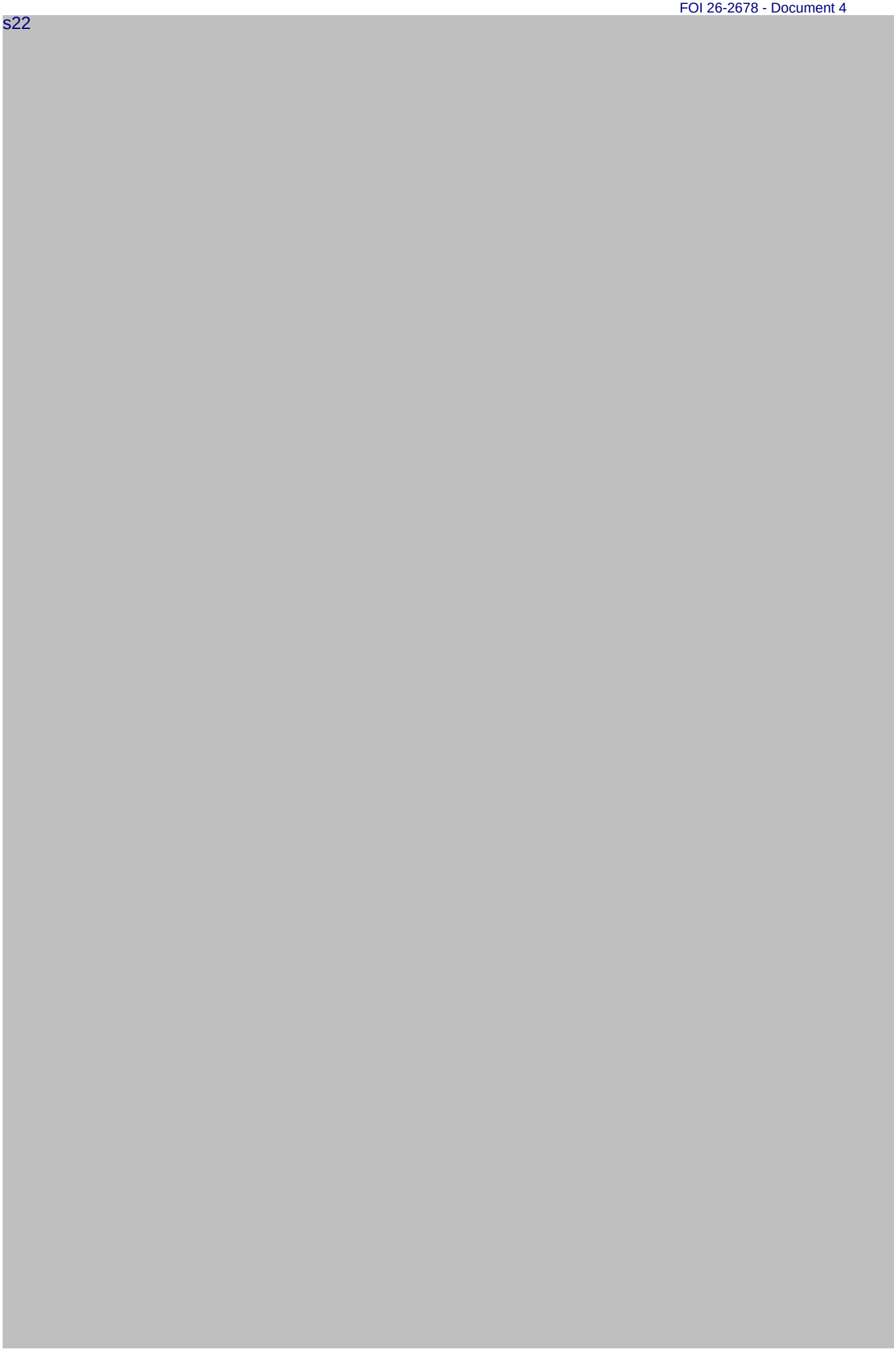


APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Pharmacovigilance Inspection Plan

Sponsor name:	s22
Sponsor address:	s22
Inspection type:	Routine systems-based (Remote)
Inspection dates:	s22 2023
Inspectors:	s22 (lead inspector), s22 (co-inspector), s22 (co-inspector)

Time (AEST)	Activity	Staff involved
	PRE-INSPECTION CALL s22 *2023*	
10 – 11am	*Pre-inspection meeting* • Inspection logistics • Testing audio, video, screen sharing • Q&A	*TGA* s22 *Sponsor Staff* • s22
	DAY 1 (remote) s22 *2023*	
9:30 – 10.45am	*Opening meeting* • Introductions • Attendance • Scope • Confirmation of Inspection Plan	*TGA* s22
	Company Presentation Overview of the company and pharmacovigilance system (~30 mins)	*Sponsor Staff* • s22
	Break	
11am – 1pm	**Case collection** • Spontaneous sources of data • Solicited sources of data	*TGA* s22 *Sponsor Staff* • s22

Time (AEST)	Activity	Staff involved
		• s22
1pm – 2pm	**Lunch/Break**	
2:00 – 4:00pm	**Review of procedures for the management of:** • Case entry • Case management • Follow-up • Quality assurance **Expedited reporting of adverse drug reactions to the TGA**	*TGA* s22 *Sponsor Staff* s22
	DAY 2 (remote) s22 *2023*	
9.30 – 11.30am	**Maintenance of Reference Safety Information** • Overview of the management of variation requests (Sponsor and TGA initiated) • Process for the updating PI and CMIs following the identification of new safety information • Implementation of PIs and CMIs following approval • Minimum PI, Package inserts and label • Maintenance of standard response and FAQ for medical information	*TGA* s22 *Sponsor Staff* s22
1:00 – 2:00pm	**Lunch/Break**	
2:00-4.00pm	**Ongoing monitoring**	*TGA* s22

Time (AEST)	Activity	Staff involved
	Management and reporting of significant safety issues to the TGA	s22 **Sponsor Staff** s22
	DAY 3 (remote) s22 *2023*	
9:30 - 11am	**Post-approval pharmacovigilance commitments** • Conditions of registration • RMPs • PSURs Management of product related promotional / education material	*TGA* s22 *Sponsor Staff* s22
	DAY 4 (remote) s22 *2023*	
10am	**Cut-off for document delivery for the closing meeting**	
4.00pm	*Closing meeting*	*TGA* s22 *Sponsor Staff* s22

Time (AEST)	Activity	Staff involved
		• s22

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
APSS	Australian Pharmacovigilance System Summary
s22	
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
ATSI	Aboriginal or Torres Strait Islander
BCP	Business continuity plan
BTS	Black Triangle Scheme
CAPA	Corrective and Preventative Action
CCDS	Core Company Data Sheets
CCSI	Core Company Safety Information
s22	
CMI	Consumer Product Information
DHPC	Dear Healthcare Professional Communication
s22	
eCTD	electronic Common Technical document
EMA	European Medicine Agency
FDA	Food and Drug Administration
GSD	Global Safety Database
s22	
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
IME	Important Medical Event
s47G(1)(a)	
MI	Medical Information
MKR	Market Research project
MSA	Master Services Agreement
ODCS	organised data collection system
s22	
PAC	Post-approval commitments
PI	Product Information
PQC	Product Quality Complaint
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreement
PVIP	Pharmacovigilance Inspection Program
QMS	Quality Management System
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
RMP	Risk Management Plan
RSI	Reference Safety Information
SAR	Serious adverse reaction
SDEA	Safety Data Exchange Agreement
s22	
SOP	Standard Operating Procedure
SSR	Safety Related Request
SSI	Significant Safety Issue
TGA	Therapeutic Goods Administration

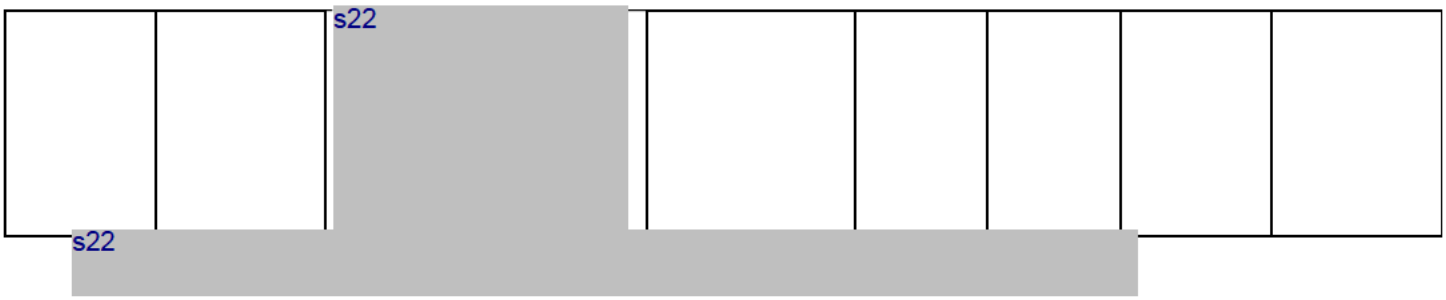
APPENDIX IV: MAJOR DEFICIENCY 3.1

Sponsor Case ID	Date received by sponsor (Day 0) as per the source document	Suspect product(s)	Reaction terms (MedDRA Pt) per sponsor report to the TGA	TGA submission date	Delay (days)
s22					12
					30
					28
					1
					17
					1
					27
					19
					9

s22	
	17
	33
	33
	8

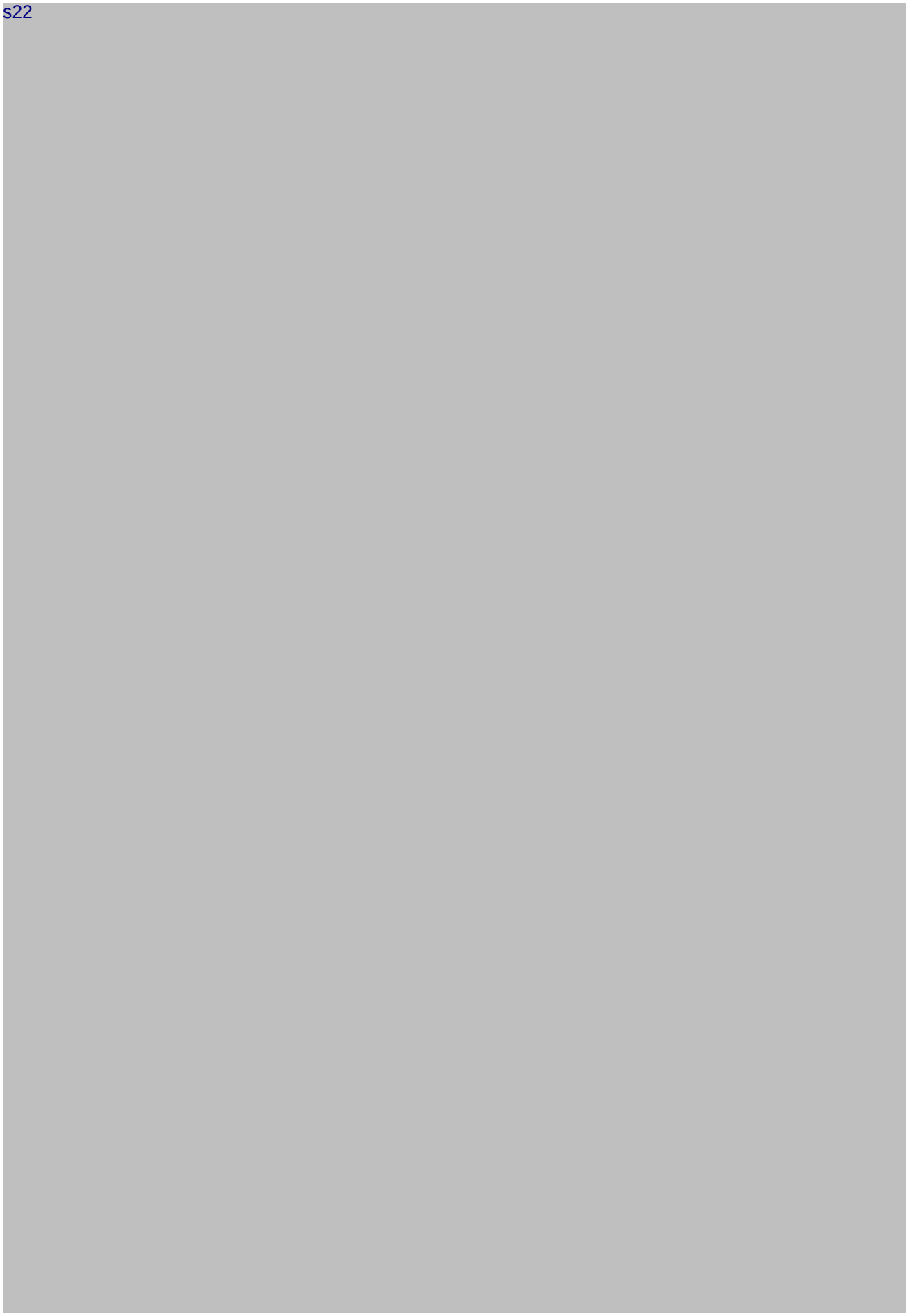
APPENDIX V: MAJOR DEFICIENCY 3.2 s22

Day 0	Suspected Product(s)	Verbatim description from article	MedDRA Event terms	Serious?	Patient	Due date to the TGA	Delay to the TGA (days)
s22							392 days as of Inspection Day 4


s22
s22

APPENDIX VI MAJOR DEFICIENCY 4.1

Products	SDEA Partner	Country of SDEA Partner	Date of SDEA / Version	Database responsibilities according to the SDEA	Responsibility and timeline for provision of Australian serious cases with the sponsor	Responsibility and timeline for provision of Australian non-serious cases, invalid cases and non-serious special situation cases with the sponsor
s22						


s22

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22

RE: TGA Pharmacovigilance Inspection of s22

Please find attached the inspection report for the remote pharmacovigilance inspection of s22 s22, conducted by the Therapeutic Goods Administration (TGA) on s22 2023.

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*. The purpose of the inspection was to assess compliance with the relevant pharmacovigilance legislation and guidelines and the conditions specified in the relevant approvals for registration or listing on the Australian Register of Therapeutic Goods (ARTG), and any subsequent variations.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as Appendix I).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Commitment Tracker.

For certain deficiencies, including all major and critical deficiencies, you are requested to submit objective evidence of corrective or preventive actions after their completion dates.

Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed. In some circumstances, a re-inspection may be required to ensure completion of such activities.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Senior Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22 2023

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor address:	s22 .
Main site contact:	s22 and Australian Pharmacovigilance Contact Person
Inspection type:	Routine, systems-related inspection
Method of inspection:	Remote
Inspection scope:	To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines
Inspection date/s:	s22 2023
Inspector/s:	s22 (Lead), s22 (Co-inspector), s22 (Co-inspector)
Inspection finding summary:	0 Critical Deficiencies 2 Major Deficiencies s22
Date report issued to sponsor:	s22 2023
Reference:	D23-3543213

Contents

s22

s22 [redacted]

s22 [redacted]

Introduction

s22 was selected for a routine inspection as part of the TGA's Pharmacovigilance Inspection Programme (PVIP); all acronyms used in this report are listed in Appendix III. The purpose of the inspection was to review compliance with currently applicable Australian pharmacovigilance (PV) regulations and guidelines. In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021) (*Pharmacovigilance Guidelines*)*
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

s22

Company background:

s22 (sponsor), located in s22, was established in s22 and is also responsible for business operations in s22 and may also be referred to as s22. The sponsor is an affiliate of s22, a global pharmaceutical company headquartered in the s22 with approximately s22 employees worldwide and medicines marketed in s22 countries. The sponsor employs approximately s22 employees across s22 and specialises in s22 products across s22 main product areas: s22

PV activities are the responsibility of the s22 organisation with responsibilities shared between s22 groups; s22 .

PV activities performed by s47G(1)(a) include:

- Compilation of Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs)
- Signal detection and management
- Assessment of Significant Safety Issues (SSI)

PV activities performed by s47G(1)(a) include:

- Data entry and coding and evaluation
- Global literature search/review

PV activities performed by the s47G(1)(a) (responsibilities shared between the s47G(1)(a) include:

- Case intake
- Case follow up
- Reconciliations
- Serious adverse reaction (SAR) reporting to the TGA
- PSUR and RMP submission to the TGA
- Assessment and submission of SSIs
- PV training
- Execution of additional risk minimisation activities.

Various vendors were also used to support company s47G(1)(a) such as literature surveillance, case management and pharmacoepidemiology.

The s22 team in Australia is composed of s22 staff, the s22 team had s22 staff and both teams reported to the s22 who was also the Deputy Qualified Person for Pharmacovigilance (QPPVA).

The sponsor had s22 medicines entered in the Australian Register of Therapeutic Goods (ARTG) for supply in Australia at the time of the inspection. s22 of these products, s22 provisionally registered. Within the sponsor product portfolio, there are s22 products requiring RMPs and s22 products with ongoing PSUR submissions to the TGA. s22 sponsor products had inclusion in the Black Triangle Scheme applied as a specific condition of registration.

The sponsor contracted a third party s22 in Australia. s22 and a number of s22 delivered by third party vendors were ongoing in Australia at the time of the inspection. s22 interventional post-authorisation study sponsored by the sponsor (s22 was ongoing in Australia at the time of the inspection as well as s22 non-interventional post-authorisation sponsored studies.

Brief report of the inspection activities undertaken

Scope of inspection

The inspection was conducted remotely via videoconference and included a review of both local and global PV systems. Company personnel from Australia, s22 and s22 attended the inspection via videoconference.

The inspection was conducted through interviews and review of documents, including searches of PV, Medical Information (MI) and product quality complaint (PQC) databases. The PV topic areas reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II) and included a review of:

- the collection, management and reporting of spontaneous and solicited adverse reaction (AR) reports
- ongoing safety evaluation and the management of SSIs
- the management of reference safety information (RSI)
- the management of PV post-approval commitments (PAC)
- the role of the Australian Pharmacovigilance Contact Person (A-PVCP) and QPPVA
- the quality management system (QMS).

Documents submitted prior to the inspection

The company submitted an 'Australian Pharmacovigilance System Summary' (APSS) document on s22 2023 to assist with inspection planning and preparation. Other specific documents including PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the company prior to the inspection.

Conduct of the inspection

The inspection was conducted in accordance with the Inspection Plan (attached as Appendix II).

Tabulated Summary of Inspection Deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing and reporting ARs and special situation reports received from spontaneous and solicited sources, were reviewed during the inspection. This included a review of all Australian reports received by the company between s22 When required, the narrative and source documentation for specific cases were analysed. s22
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of company products were reviewed during the inspection. s22
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the inspection. Deficiencies related to the management and reporting of SSIs are described in Major Deficiency 1.
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the inspection. s22
Management of PAC	The procedure for managing PV PAC, including submission of PSURs, maintenance of RMP documents and implementation of RMP commitments, was reviewed during the inspection. Deficiencies related to the management of PAC are described in Major Deficiency 2.
A-PVCP and QPPVA	During the inspection, the roles and responsibilities of the A-PVCP and QPPVA were reviewed including sponsor compliance with associated reporting obligations. s22
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and SOPs, was reviewed during the inspection. s22

List of deficiencies identified during the inspection

Critical deficiencies

Nil critical deficiencies were identified during the inspection.

Major deficiencies

1. Deficiencies in management and reporting of SSIs

1.1. Systematic failures to conduct SSI assessments of safety related actions by Comparable Overseas Regulators (CORs) resulting in missed SSI notifications to the TGA

In accordance with the *Pharmacovigilance Guidelines*, You **MUST** report all significant safety issues related to your medicine within 72 hours of awareness. Where you have a global parent company, you need to be confident that your SOPs will ensure you become aware of international safety information and regulatory actions in a timely manner.

Examples of significant safety issues include safety-related actions by comparable international regulatory agencies such as
– the withdrawal or suspension of the medicine's availability
– the **addition or modification, for safety reasons, of a contraindication, warning or precaution statement to the product information** or label
– the modification or removal, for safety reasons, of an indication.

All pertinent factors should be taken into account when assessing a safety issue. Issues to consider include the medicine, the risks involved and the regulatory context. Further, **a safety issue leading to international regulatory action is considered to be significant and hence reportable regardless of whether you agree with the recommendations and conclusions of the international regulator.**

If you determine after appropriate assessment that a safety issue is not significant and do not report it, you should document a justification for this decision. We may ask you to provide this documentation at any time.

s22 safety-related actions by CORs as summarised in the table in Appendix IV were not assessed as an SSI nor notified to the sponsor in Australia. The sponsor also informed that evidence of the decision not to classify these safety issues as an SSI was not available. In addition to this non-compliance of a failure to document the SSI assessment and justification for not reporting, s22 examples also constituted missed SSI notifications to the TGA. All identified examples were related to COR requests for the addition or modification of warning or precaution statement(s) in the PI for safety reasons.

Whilst the exact delay to the TGA for each example of a missed SSI notification could not be calculated since the safety issue was not communicated to the sponsor (Day 0),it was noted that the examples spanned the s22 period between s22 . The first example was received to the s22 organisation on s22 and the latest example received on s22

The justification for not notifying the TGA of these SSIs centred on the safety issue not qualifying for notification to the sponsor as per global SOP, s47 . This indicated that the global procedure did not facilitate compliance with the TGA requirements. s22 examples were received and managed by the s22 after s22 This is notable since procedure s47G(1)(a) was updated on s22 to specifically include assessment of safety issues as SSIs in line with the *Pharmacovigilance Guidelines.*

In some instances, the sponsor added that Australian PI already contained these warnings and precautions. However, this rationale was not substantiated for most examples since the request from the COR included additional information or a modification that was not reflected in the Australian PI. Further detail is provided for each example in table in Appendix IV.

1.2. Deficiencies in the timeline of notification of safety issues from global company to the sponsor

In accordance with the *Pharmacovigilance Guidelines*, where you have a global parent company, you need to be confident that your SOPs will ensure you become aware of international safety information and regulatory actions in a timely manner.

Examples of significant safety issues include safety-related actions by comparable international regulatory agencies. A safety issue leading to international regulatory action is considered to be significant and hence reportable regardless of whether you agree with the recommendations and conclusions of the international regulator.

During the inspection, a review of safety issues managed for sponsor products over a s22 period identified two examples of safety issues which qualified as an SSI according to the *Pharmacovigilance Guidelines* and were notified by the global organisation to the local sponsor in 24 days and 142 days which was not considered timely. These examples were associated with s22 and are outlined in the table below.

High level description of the signal/safety issue	Date of first company (local or global as applicable) awareness of the issue	Date of local sponsor awareness of validated signal/safety issue (Day 0)	Date reported to the TGA	Days between signal validation and local sponsor awareness
s22				24
				142

*sponsor informed that this was not communicated to the TGA in the context of an SSI

The sponsor rationale for the timeframe of communication of the validated signal to the sponsor was reviewed but did not substantiate the non-timely communication to the sponsor. Sponsors are required to assess safety issues and notify SSIs to the TGA in an expedited manner and for relevant safety related actions by CORs, regardless of whether you agree with the recommendations and conclusions of the international regulator.

1.3. Deficiencies in timeliness of SSI assessment of internally identified validated signals

In accordance with the *Pharmacovigilance Guidelines*, a significant safety issue is a new safety issue or **validated signal** considered by you in relation to your medicines that requires urgent attention of the TGA.

> If you determine after appropriate assessment that a safety issue is not significant and do not report it, you should document a justification for this decision. We may ask you to provide this documentation at any time.

Review of company procedures associated with management of validated signals revealed that SSI assessments of such safety issues were not conducted in a timely manner.

Since s22 , a subset of validated signals (considered to be - possible SSIs from any source) would undergo an SSI assessment by the EU QPPV or delegate at the signal prioritisation stage in accordance with global procedure, s47 All other validated signals underwent an SSI assessment by the sponsor PV Team upon receipt through the communication process outlined in s47 This procedure described that communication of internal signals to affiliates that require submission of internal signals to their regulatory agency occurs only upon completion of the signal evaluation, documentation of the signal evaluation outcome, and once the s47G(1)(a) is approved and available to be uploaded to the s47G(1)(a) site. Given the company target timeline for completion of routine signal evaluations was 60 days after validation, the SSI assessment of internally identified validated signals that were not in scope of procedure s47 was not conducted in a timely manner.

This process was not aligned with the *Pharmacovigilance Guidelines* since the Guidelines defined that an SSI is a validated signal (not evaluated signal) considered by you in relation to your medicines.

In addition, whilst it is acknowledged that the procedure s47 was effective prior to s22 s22 , at that time the process concerned Emerging Safety Issue (ESI) assessment only as per the EMA Guideline GVP Module IX. An ESI has a different scope to an SSI. Therefore prior to s22 , there was no timely SSI assessment process for any internally identified validated signal.

1.4. Deficiencies in the documentation of the justification of SSI assessment

> In accordance with the *Pharmacovigilance Guidelines*, if you determine after appropriate assessment that a safety issue is not significant and do not report it, you should document a justification for this decision. We may ask you to provide this documentation at any time.
>
> We expect you to use your professional judgement in determining whether a safety issue is significant (...) and it is up to you to assess safety issues on a case-by-case basis and evaluate whether this has an impact on the medicine's safety or benefit-risk balance and/or implications for public health. All pertinent factors should be taken into account when assessing a safety issue. Issues to consider include the medicine, the risks involved and the regulatory context.
>
> Develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved. You should make provisions for regular review for improvements to the system where required.

Deficiencies were identified in the sponsor process for the documentation of SSI assessment and the documented justification for a non-SSI assessment conducted by the local sponsor and global organisation. Justifications were either not provided or did not always show that all pertinent factors as described in the *Pharmacovigilance Guidelines* had been considered.

The sponsor s47G(1)(a) were responsible to make an SSI assessment of safety issues notified to them by the global organisation or other safety issues that they became aware of. The assessment was documented in the local tracker, "s47 ",

and the sponsor informed that this tracker was the repository for recording assessments including any rationale for the decision. However, the justification for the decision was not consistently recorded. Examples are provided below.

In the period, s22 , sponsor assessments of s22 safety issues that did **not** result in an SSI notification to the TGA were recorded in the Tracker, however:

- The field "s47G(1)(a) " included a justification for the assessment for s47G(1) entries only.
- The field "s47G(1)(a) " sometimes included evidence of an Australian specific impact assessment and sometimes included only high level information such as, "s47G(1)(a) " and "s47G(1)(a) with no further documented assessment.

It was noted that the local procedure s47 described the activity s47 but did not specify the requirement to document the justification for the decision when a safety issue was assessed as not significant. It was not clear whether the field "s47G(1)(a) " in the tracker pertained to the s47G(1)(a) or the s47G(1)(a) of the s22 since sometimes Australian specific context was tracked there and sometimes it was tracked in the "s47G(1)(a) " field. In summary, the sponsor processes that underpinned the sponsor SSI assessment of safety issues were found to be deficient.

Since s22 , the Global procedure, s47 included a responsibility for the s47G(1)(a) to assess a potential emerging/significant safety issue to determine whether the issue qualifies as an emerging/significant safety issue. SSI was defined in this procedure as an issue defined in the TGA *Pharmacovigilance Guidelines*. However, the justification for the assessment of safety issues as non-SSIs was not explicitly recorded in the s47G(1)(a) which was the system used to manage all safety observations and safety signals. Whilst current procedure s47 , outlined instructions for fields in the s47G(1)(a) for:

- EU Emerging Safety Issue Determination
- Date of EU Emerging Safety Issue Determination, and the
- Rationale if not considered an EU Emerging Safety Issue

there were no equivalent fields associated with the SSI assessment.

The sponsor informed that this was likely due to procedure s47 not yet having been updated following the expansion in scope of procedure, s47 earlier this year.

1.5. Deficiencies in sponsor oversight of SSI assessments (made by global organisation)

In accordance with the *Pharmacovigilance Guidelines*, the QPPVA needs to have adequate understanding of the Australian and global pharmacovigilance processes in order to allow them to have effective oversight of the entire pharmacovigilance system. Where you have a global parent company, you need to be confident that your SOPs will ensure you become aware of international safety information and regulatory actions in a timely manner.

Sponsors should develop clear written standard operating procedures (SOP) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

During the inspection it was identified that the QPPVA did not have access to the SSI assessments made at the global organisation level since s22 under the procedure, s47 (if the safety issue was determined not to be an SSI).

Whilst it is acknowledged that company processes facilitated the subsequent communication of all safety issues, via procedure s47 and that the QPPVA would then conduct an SSI assessment locally in Australia, it is recommended that the QPPVA has access to all SSI assessments for effective oversight of the Australian PV system.

In addition, the non-compliance described in Major Deficiency 1.1 provided evidence that the QPPVA did not have effective oversight of the management of safety issues at the global organisation level since the s22 examples were not provided to the sponsor.

1.6. Non-compliance associated with a documented sponsor SSI assessment

In accordance with the *Pharmacovigilance Guidelines*, if you determine after appropriate assessment that a safety issue is not significant and do not report it, you should document a justification for this decision. We may ask you to provide this documentation at any time.

A review of the local tracker, "s47 " during the inspection revealed that the SSI assessment of a validated signal for s22 communicated to the sponsor on s22 , was assessed s22 based on the verbatim recorded assessment.

The sponsor recorded the date of the SSI assessment by s47G(1)(a) as s22 in the tracker. The sponsor informed during the inspection that whilst there was no defined timeline for local SSI assessment following awareness of a safety issue, an assessment would always be made within 72 hours to facilitate the on time reporting of any safety issues assessed to be an SSI. On s22 72 hours after receipt of this validated signal, the current version of the *Pharmacovigilance Guidelines* was Version 2.2, effective January 2021. s22

2. Deficiencies in management of PAC

2.1. Deficiencies in notification of the commencement of supply to the TGA

In accordance with the conditions of registration, the actual date of commencement of supply **MUST** be notified to the Head, Prescription Medicines Authorisation Branch, TGA. Should the sponsor decide not to proceed to supply, notification to this effect should be provided.

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

2.1.1. Failure to notify the TGA of commencement of supply (until inspection)

During the inspection, sponsor compliance with the condition of registration to notify the TGA of the date of commencement of supply was reviewed and it was identified that this condition was not consistently fulfilled for all applicable sponsor medicines.

Evidence of notification to the TGA of commencement of supply for the following four medicines was not available at the time of TGA request on s22

Product (ARTG No.)	Date of commencement of supply	Date of TGA notification of	Time from commencement of

		commencement of supply	supply to TGA notification (days)
s22			2403
			1822
			1771
			1354

The sponsor informed s47G(1)(a) ". The sponsor subsequently fulfilled the notification to the TGA of the commencement of supply for these products on s22 .

This deficiency may have been attributed in part to the lack of a formal written procedure that explicitly described the legal responsibility to notify the TGA of the commencement of supply.

It was noted that Version s47G(1) of a s47G(1)(a) However, this was a non-mandatory local job aid and was not associated with any SOP trained upon by s47G(1)(a) team members. A completed example of the checklist was requested for a sample of two products (s22) but was only available for s22 . The sponsor justified that different approaches may be adopted by the team members depending on their level of experience/ preference.

The recent changes to the management of this PAC were acknowledged in the inspection. Since s22 , the sponsor commenced tracking the requirement to notify the TGA of the commencement of supply within the s47G(1)(a) system for all new registrations. The commitment is entered with a projected "due date" for the activity, in line with the date of anticipated s22 . The s47G(1)(a) system will prompt awareness of open activities to s47G(1)(d) users via s47G(1)(a) to facilitate oversight of compliance with this PAC. Furthermore, there were quality control (QC) steps in place via s22 to ensure that all PAC, including the requirement to notify the TGA of the commencement of supply were entered accurately into s47G(1)(a) via review by a s47G(1)(a) . It was confirmed that prior to the implementation of s47G(1)(a) to manage this PAC, there was no tracking system implemented to facilitate oversight of compliance.

2.1.2. Inaccurate information provided to the TGA regarding first supply date of s22

An example of provision of inaccurate information regarding the commencement of supply date for s22 was identified during the inspection. This related to separate communications sent to the TGA by the sponsor s47G(1)(a) and s47G(1) teams on this topic. The details are outlined in the table below.

Date of sponsor communication	Sponsor team	TGA recipient	Information communicated
s22			

s22

It was verified in the inspection that the two communications to the s47G(1)(a) were accurate whereas the information provided to the s47G(1)(a) was inaccurate.

This deficiency may have been attributed to the fact that there was no formal tracking by s47G(1)(a) of the commencement of supply PAC prior to s22 (as discussed in the previous deficiency) when this commitment started to be tracked in the s47G(1)(a) system for new registrations. During the inspection the QPPVA confirmed their current access to the s47G(1)(a) system.

2.2. Late submission of PSURs to the TGA

In accordance with the conditions of registration, sponsors **MUST** submit PSURs to the TGA in line with the timeframes and frequency specified in the approval letter.

The *TGA Pharmacovigilance obligations of medicine sponsors - frequently asked questions* outline, if you are required to submit PSURs to the TGA, the frequency will be outlined as a specific condition of registration under section 28(2B) of the *Therapeutic Goods Act 1989*. For products that are approved in the European Union (EU), the TGA will usually align the PSUR reporting requirements and timeframes with those required by the European Medicines Agency (EMA). In this case, the specific condition of registration will state that PSUR reports are to align with the current EU reference date (EURD) list, which are published on the EMA website. Sponsors are expected to provide PSURs to the TGA consistent with all elements described in the EURD list, including: PSUR submission frequency, Data lock point and PSUR submission due date (according to the timelines defined in GVP Module VII, Section A).

The EURD list is frequently updated by the EMA. Therefore, sponsors with this specific condition are expected to have a process for periodically checking the current EURD list to ensure that internally tracked PSUR reporting requirements are updated accordingly.

A review of sponsor PSUR submissions for a sample of products revealed three delayed submissions of PSURs for s22.

Approval letters for s22 and the approval letter for s22 included the following specific condition of registration:

s22

Details of these delayed submissions are outlined in the table below.

Product, period covered	Data Lock Point (DLP)	Submission due date*	Submission Date	Delay (days)	Sponsor comment
s22				66	Reason for late submission is not known. The PSUR was available in a timely manner from the s47G(1)(a) team but submission by s47G(1)(a) was delayed.
				24	Submission of this PSUR was 4 days after the 90 calendar days from DLP. This occurred due to

					an error in the scheduling by the s47G(1)(a) and was documented in s47G(1)(a) The PSUR was available in a timely manner from the s47G(1)(a) team but submission by s47G(1)(a) was delayed.
s22				10	Submission was on time: this was submitted within 90 calendar days of the DLP.

* based on the EURD list, submission due date within 70 calendar days of the DLP (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months).

It was also noted that the sponsor had applied a PSUR due date to the TGA of within 90 calendar days of the DLP for these submissions whereas the correct timeframe for submission was within 70 calendar days of the DLP, in accordance with the approval letters.

2.3. Non-submission of updated RMP-ASAs to the TGA (following EMA approval of changes to the summary of safety concerns in the EU -RMP)

In accordance with the TGA *Guidelines on Risk management plans for medicines and biologicals*, *March 2019*, sponsors **MUST** submit an updated RMP and/or ASA when the TGA request it and whenever there is significant change, such as: **when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.**

For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the request of the TGA, then we recommended that the updated RMP/ASA is **submitted within 3 months of the change being accepted by the EMA.**

Inspector review of a sample of s22 current EU-RMPs against the corresponding current RMP/Australian Specific Annex (ASA) provided to the TGA, revealed that all s22 RMP/ASAs were outdated and that previous significant changes to the EU-EMP, accepted by the EMA, had not been submitted to the TGA as an updated RMP/ASA. The delays in these examples occurred following the EMA acceptance of changes to the summary of safety concerns. Further information regarding these examples is summarised in Appendix V.

2.4. Delayed submission of updated RMP/ASAs to the TGA (following EMA approval of changes to the summary of safety concerns in the EU -RMP)

In accordance with the TGA *Guidelines on Risk management plans for medicines and biologicals*, *March 2019*, sponsors **MUST** submit an updated RMP and/or ASA when the TGA request it and whenever there is significant change, such as: **when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.**
For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the request of the TGA, then we recommended that the updated RMP/ASA is **submitted within 3 months of the change being accepted by the EMA**.

In accordance with the *Pharmacovigilance Guidelines*, We require you to have an **effective** pharmacovigilance system in place in order to meet all pharmacovigilance requirements described in these guidelines and applicable legislation. The QPPVA needs to have adequate

understanding of the Australian and global pharmacovigilance processes in order to allow them to have **effective oversight** of the entire pharmacovigilance system.

It was identified during the inspection that out of a sample of the last s22 RMP/ASA submissions to the TGA, all s22 were submitted with a delay outside the recommended 3-month timeframe. The delays occurred following the EMA approval of changes to the EU-RMP which included changes to the summary of safety concerns. Further information regarding these examples is summarised in the table in Appendix VI.

Whilst it is acknowledged that the sponsor had identified some of these examples of non-compliance ahead of the inspection (delayed s22) and recorded these in a deviation s22 which was managed in a timely way (date of discovery, s22 completion date s22 the sponsor had not conducted a root cause analysis / investigation as part of this deviation. The sponsor confirmed that no formal root cause investigation was required for the deviation based on the level s47G(1)(a) assigned to the deviation (per procedure s47).

As an outcome of the deviation, the updated RMP/ASAs were submitted to the TGA, and an action was assigned to the s47G(1) team to create a tracker for oversight of current RMP/ASA versions, assessments, and future submission dates. However, it was confirmed during the inspection that the tracker was not maintained, there was no associated written procedure that described the use of this tracker within the sponsor PV system and there was no current tracker to keep oversight of RMP/ASAs in Australia. The sponsor utilised the s47G(1)(a) system to track actual submissions of all new or updated EU-RMP or ASAs to the TGA only.

It was noted that the sponsor assessment of the criticality level of deviation s47G(1)(a) documented,

s47G(1)(a)

However, there was no consideration in this assessment of whether the deviation represented a one-off or systematic non-compliance in the sponsors PV system. In addition, the statement that s47G(1)(a) was incorrect.

Moreover, the late RMP/ASA submissions of the other two examples outlined in this deficiency (for s22 occurred after the completion of this deviation. No further deviation was created in association with the late submission of the s22 RMP/ASA. Whilst a deviation (s47G(1)(a)) was created in association with the s22 RMP/ASA submission, the deviation was focused on the s47G(1)(a) (refer to Major Deficiency 2.6) and s47G(1)(a) did not identify that the scope of the deviation should have been broadened to cover the late submission of an EU-RMP update. Therefore, no further preventative actions were implemented to prevent ongoing reoccurrence of this non-compliance nor to assess the effectiveness of the previous CAPA.

2.5. Non-timely communication of EMA accepted EU-RMP to the sponsor from global headquarters

In accordance with the TGA *Guidelines on Risk management plans for medicines and biologicals*, *March 2019*, sponsors **MUST** submit an updated RMP and/or ASA when the TGA request it and whenever there is significant change, such as: **when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.**

For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the

request of the TGA, then we recommended that the updated RMP/ASA is **submitted within 3 months of the change being accepted by the EMA.**

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and **timelines** are well-defined and understood by all personnel involved.

The EMA acceptance/approval of the updated EU-RMP s47G(1 for s22 was communicated to the sponsor by the s47G(1)(a) on s47G(1)(a), however the date of EMA approval was s47G(1)(a). Given the notification to the sponsor of the updated EU-RMP occurred more than four months after the EMA approval, it was not possible for the sponsor to fulfil the TGA recommendation of submission to the TGA of significant changes to the EU-RMP within three months of the EMA approval. EU-RMP s47G(1 for s47G(1)(a) was required to be submitted to the TGA and the submission occurred with a delay as described in Major Deficiency 2.5.

The sponsor described the expectation that the communication by the s47G(1)(a) of EMA approved EU RMPs to the sponsor occurs in a timely fashion, with a best practice of s47G(1)(a). However, no formal timeline was specified in the current version of the governing procedure, s47 .

2.6. Failure to communicate alteration to risk min activity in Australia in line with the TGA Guidelines on Risk management plans for medicines and biologicals

In accordance with the TGA *Guidelines on Risk management plans for medicines and biologicals*, sponsors **MUST** submit an updated RMP and/or ASA (…) whenever there is a significant change, such as (…) if you propose to cease an additional risk minimisation activity. You should seek agreement from the TGA before prematurely ceasing or significantly altering additional risk minimisation that is being undertaken in Australia.

It was identified through a review of the last RMP/ASA update to the TGA for s22 that the sponsor failed to consult with the TGA about changes s47G(1)(a) before implementing the changes. Furthermore, the updated RMP/ASA that described these changes was not submitted to the TGA in a timely way. The lack of consultation with TGA and the delayed submission of the updated RMP / ASA, regarding the changes to the s22 represented non-compliance with the requirements and recommendations of the *Guidelines on Risk management plans for medicines and biologicals*.

The s22 ASA was updated to s47G(1)(a) and submitted to the TGA on s22. Changes in the ASA included the s47G(1)(a) from s47G(1)(a)

s47G(1)(a)

The sponsor informed during the inspection that in practice, the cessation of the provision of the s22 to s22 via ordering through the online s47G(1)(a) occurred in s22. Therefore, communication of this update to the TGA happened s47G(1)(a) after the change was implemented.

It is acknowledged that ahead of the inspection the sponsor had identified this non-compliance on s22 and documented this as a deviation to the sponsor PV system in their QMS s47G(1)(a) with a root cause "s47G(1)(a) ."

2.7. Deficiencies in procedures regarding maintenance of the ASA

In accordance with the TGA *Guidelines on Risk management plans for medicines and biologicals*, sponsors should update your risk management plan when new information becomes available regardless of whether your product is marketed. **You should ensure that you always keep your RMP and ASA up to date for your own records and because we may request an updated RMP from you at any time.**

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

Sponsors written procedures relating to ongoing review and maintenance of the RMP/ASA were found to be deficient.

The sponsor informed that the following procedures were followed in relation to the maintenance of the RMP/ASA:
s47G(1)(a)

Although the current s47 outlined the responsibility for the sponsor to s47 ", there was no standard process for recording the assessment and it was confirmed during the inspection that the sponsor assessment was conducted inconsistently.

Furthermore, it was noted that the current s47 However, the responsibility to submit an updated RMP/ASA following a change to the summary of safety concerns, including when the EMA has approved removal or reclassification of safety concerns, was not included. In addition, the procedure did not specify that the sponsor should update and maintain the ASA even when the update did not trigger a submission to the TGA and the sponsor confirmed that receipt of updated EU-RMPs did not trigger an update to the ASA, unless it was determined that a submission to the TGA of an updated ASA was required.

2.8. Non-adherence to company procedure regarding management of additional risk minimisation measures

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

The current global SOP, s47 was followed by the sponsor as a part of their PV system in relation to management of additional risk minimization activities. The SOP described the role of s47

s47 " The SOP outlined the following responsibilities for the Affiliate Implementation Team:

- **Clearly documents** (for example, in meeting minutes) s47G(1)(a) **roles and responsibilities** for the planning, implementation, tracking and reporting of additional risk minimization activities.
- **Clearly documents** (for example, in meeting minutes) **all decisions**, including any subsequent changes to local additional risk minimization activities.

s22 had active additional risk minimization activities in Australia associated with the provision of materials.

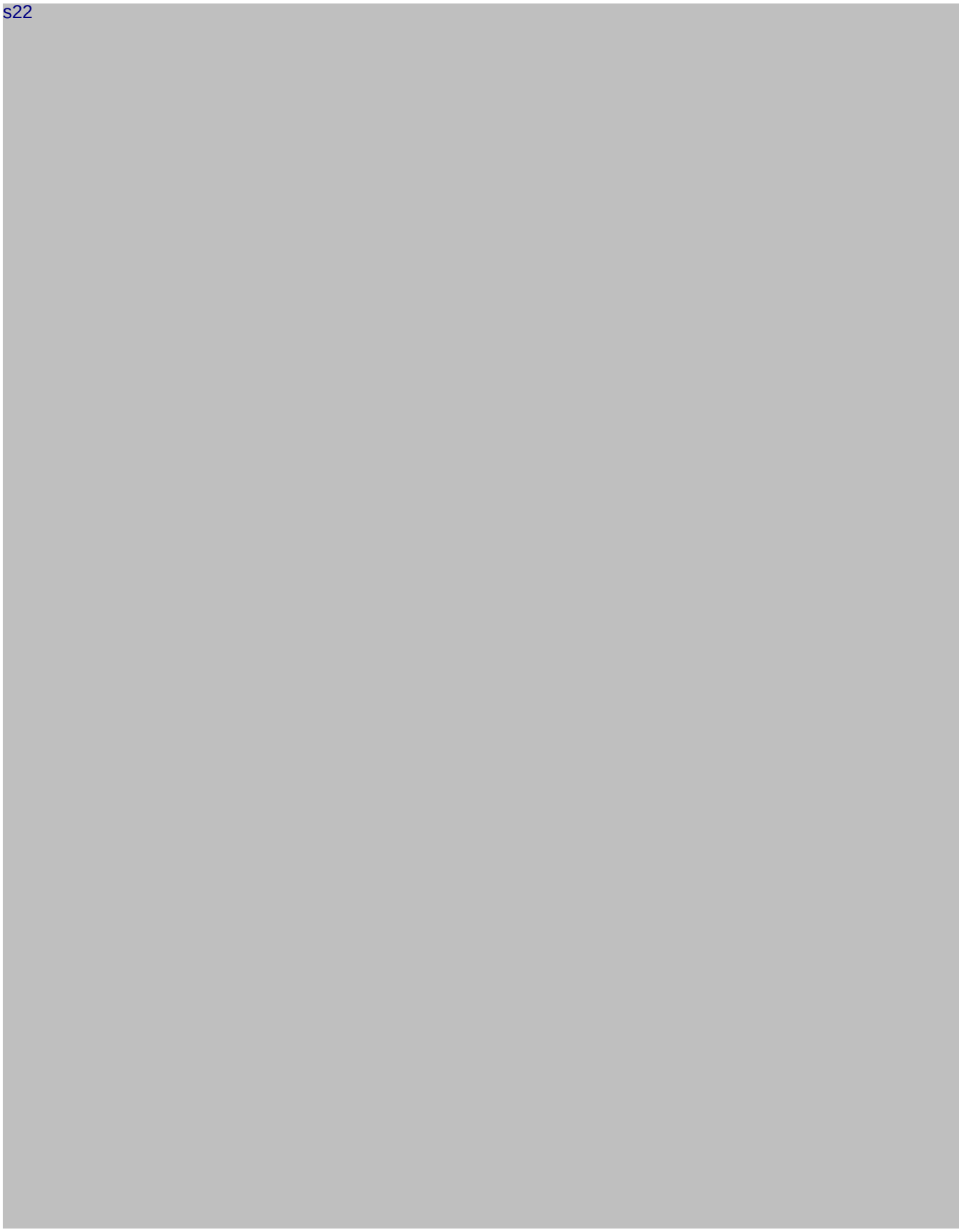
During the inspection the sponsor informed that the personnel fulfilling s47G(1)(a) roles and responsibilities as per s47 had not been documented for all products.
In addition, the following was identified regarding the documentation of decisions including any changes to agreed additional risk minimization activities in Australia:

- In relation to s47G(1)(a) an additional risk minimization activity added to s47G(1) submitted to the TGA on s47G(1)(a), the sponsor informed that "s47G(1)(a) "
- In relation to s22, an additional risk minimization activity included in the original version of the ASA s47G(1)(a) **ecisions were made but not documented at the time** regarding the changes to distribution of the s47G(1)(a) which differed to the methods described in the ASA submitted to the TGA. s22 stopped providing s47G(1)(a) and therefore stopped distributing s22 via the s47G(1)(a) in the ASA. Company decisions for the update to the ASA were only subsequently documented in sponsor s47G(1)(a) which related to the failure to notify the TGA of this alteration to the agreed additional risk minimization activity via an updated ASA submission (Refer to Major Deficiency 2.7 for further discussion on this topic).

s22

s22

s22


s22

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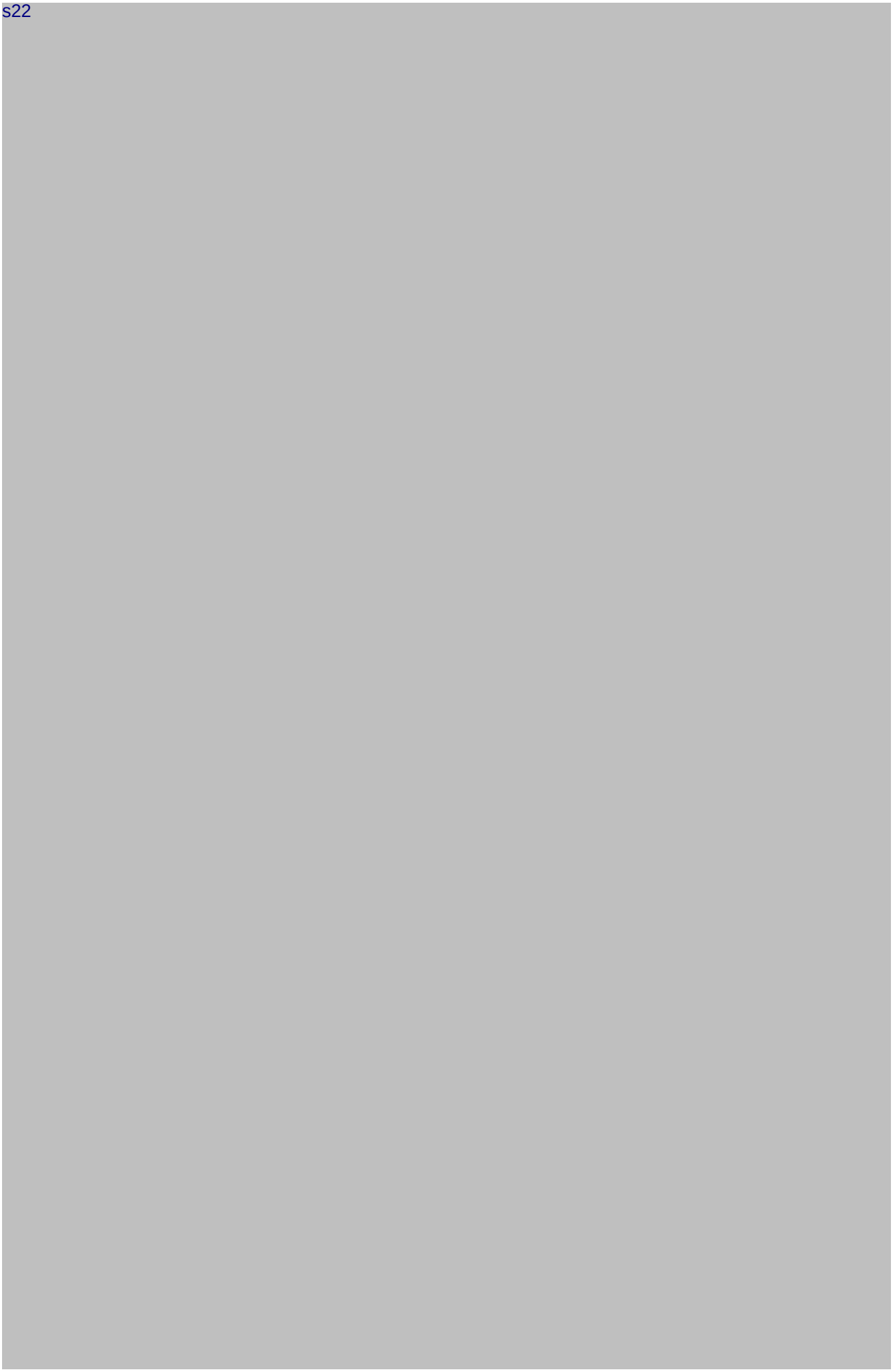
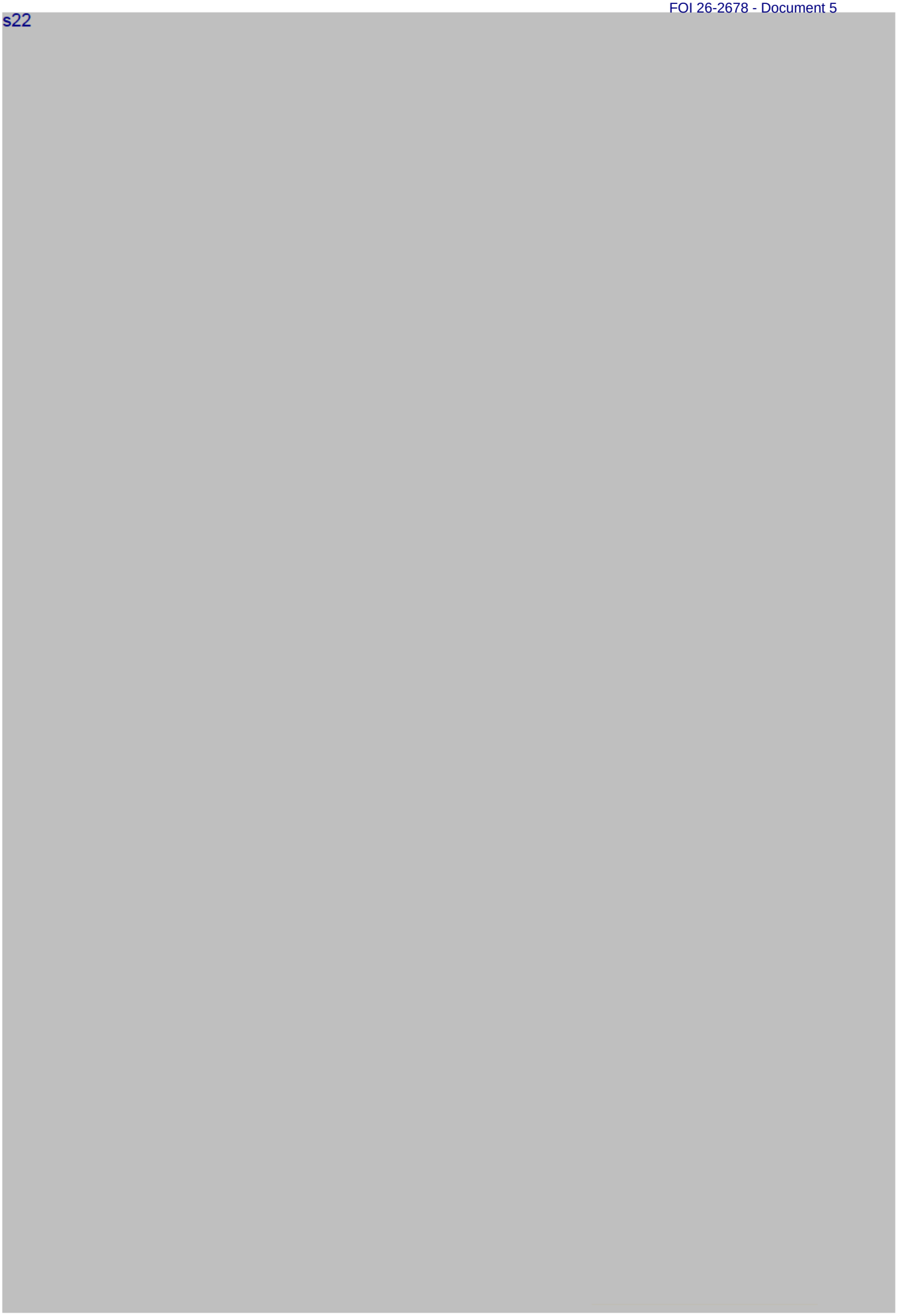


s22

s22



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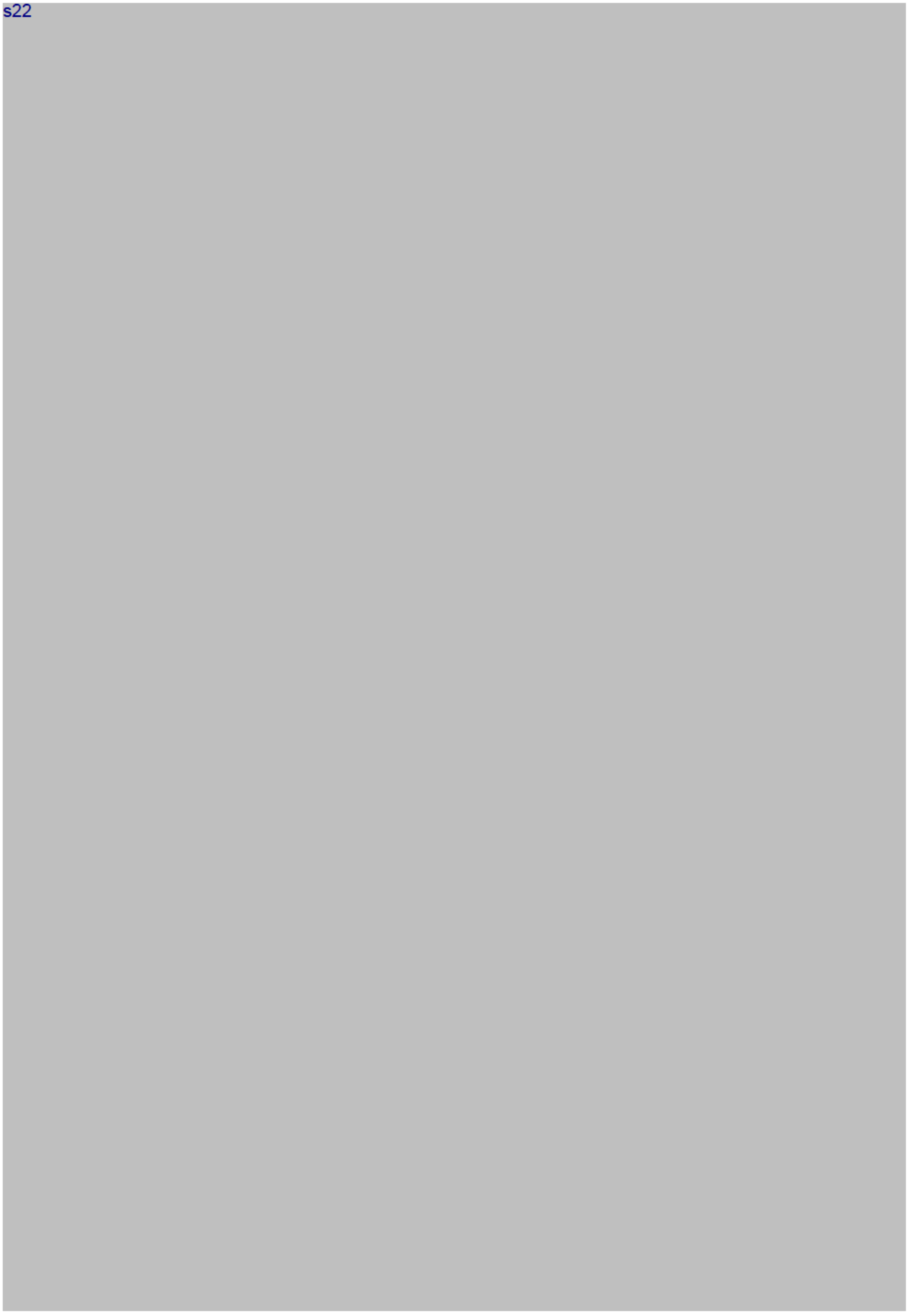

s22

s22

s22

s22

s22

APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.

- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Pharmacovigilance Inspection Plan

Sponsor name:	s22
Sponsor address:	s22
Inspection type:	Routine systems-based (Remote)
Inspection dates:	21 to 24 August 2023
Inspectors:	s22 (lead inspector), s22 (co-inspector), s22 (co-inspector), s22 (observer)

Time (AEST)	Activity	Staff involved
	PRE-INSPECTION CALL s22 *2023*	
1 – 12pm	**Pre-inspection meeting** • Inspection logistics • Testing audio, video, screen sharing • Q&A	***TGA*** s22 ***Sponsor Staff*** s22
	DAY 1 s22 *2023*	
9:30 – 10.45am	**Opening meeting** • Introductions • Attendance • Scope • Confirmation of Inspection Plan **Company Presentation** Overview of the company and pharmacovigilance system (~30 mins)	***TGA*** s22 ***Sponsor Staff*** s22

Time (AEST)	Activity	Staff involved
		s22 [redacted]
	Break	
11am – 1pm	**Case collection** • Spontaneous sources of data • Solicited sources of data	***TGA*** s22 [redacted] ***Sponsor Staff*** s22 [redacted]
1 – 2pm	**Lunch/Break**	
2-3.30pm	**Document reviews and ad-hoc interviews if required**	s22 [redacted]
3.15-3.30	**Demo of Quality Docs**	***TGA*** s22 [redacted] ***Sponsor Staff*** s22 [redacted]

Time (AEST)	Activity	Staff involved
3.30-5pm	**Review of procedures for the management of:** • Case entry • Case management • Follow-up • Quality assurance **Expedited reporting of adverse drug reactions to the TGA**	***TGA*** s22 ***Sponsor Staff*** s22
	DAY 2 s22 *2023*	
9.30 – 11.00am	**Maintenance of Reference Safety Information** • Overview of the management of variation requests (Sponsor and TGA initiated) • Process for the updating PI and CMIs following the identification of new safety information • Implementation of PIs and CMIs following approval • Package inserts and label	***TGA*** s22 ***Sponsor Staff*** s22
11.00 – 11.20	**Demo of SAIL**	***TGA*** s22 ***Sponsor Staff*** s22

Time (AEST)	Activity	Staff involved
		s22
	Break	
11.45am-1pm	**Post-approval pharmacovigilance commitments** • Conditions of registration • RMPs/ASAs • PSURs	***TGA*** s22 ***Sponsor Staff*** s22
1 – 2pm	**Lunch/Break**	
2-3.30pm	**Document reviews and ad-hoc interviews if required**	s22
3.30-5pm	**Ongoing monitoring** **Management and reporting of significant safety issues to the TGA**	***TGA*** s22 ***Sponsor Staff*** s22
	DAY 3 s22 *2023*	

Time (AEST)	Activity	Staff involved
All day	**Document reviews and ad-hoc interviews if required**	**Morning: 9:30 am - 1:00 pm** s22 **Afternoon: 2:00 pm - 5:00 pm** s22
9.30 – 9.45 am	**Demo of** s47G(1)(a) **in relation to the management of post-approval commitments**	***TGA*** s22 ***Sponsor Staff*** s22
9.45 - 10.30 am	**Interview with** s22	***TGA*** s22 ***Sponsor Staff*** s22

Time (AEST)	Activity	Staff involved
3.30 - 4pm	**Interview with Medical Information**	***TGA*** s22 ***Sponsor Staff*** s22
	DAY 4 *Thursday 24 August 2023*	
10am	**Cut-off for document delivery for the closing meeting**	
4pm-5pm	**Closing meeting**	***TGA*** s22 ***Sponsor Staff*** s22

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
APSS	Australian Pharmacovigilance System Summary
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Application Support Team
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CMI	Consumer Medicine Information
COR	Comparable Overseas Regulator
CRM	Customer Relationship Management (system)
DHPCL	Dear Healthcare Professional Letter
DLP	Data Lock Point
EMA	European Medicines Agency
ESI	Emerging Safety Issue
FDA	(US) Federal Drug Administration
s47G(1)(a)	
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
MAVIS	Medicines and Vaccines Surveillance
MI	Medical Information
MinPI	Minimum Product Information
MKR	Market Research program(s)
MSA	Master Services Agreement
PAC	Post-approval commitment(s)
PBS	Pharmaceutical Benefits Scheme
s47G(1)(a)	
PI	Product Information
PQC	Product Quality Complaint
PSP	Patient Support Program
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVIP	Pharmacovigilance Inspection Program
QC	Quality Control
QMS	Quality Management System
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
s47G(1)(a)	
RMP	Risk Management Plan
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
TBS	TGA Business Services
TGA	Therapeutic Goods Administration
s22	

APPENDIX IV: MAJOR DEFICINCY 1.1

Product	COR	High level description of request for safety-related action	Date of receipt to s22 s22 organisation	Impact to compliance with SSI notification to the TGA?
s22				Yes - this was a missed SSI notification to the TGA. The sponsor justified that the Australian PI for s22 already contained these s47G(1)(a) however the Australian PI did not and was consistent with the version of the s47G(1)(a) that the s47G(1)(a) requested to be modified on s22 s22 due to safety reasons.
				Yes - this was a missed SSI notification to the TGA. On s22 the sponsor submitted a safety variation to the TGA for the addition of s47G(1)(a) in line with a CCDS update. The safety variation included a lesser scope of safety related changes when compared to the s47G(1)(a) and did not impact the s47G(1)(a) Nevertheless, a safety variation does not substitute an SSI notification.

Product	COR	High level description of request for safety-related action	Date of receipt to s22 s22 organisation	Impact to compliance with SSI notification to the TGA?
s22				Yes - this was a missed SSI notification to the TGA. Sponsor justified that the existing Australian PI warnings s47G(1)(a) were appropriate. However, the additions s47G(1)(a) differed and provided additional information compared to the existing wording in the Australian PI. The modifications were required to be notified to the TGA as an SSI.
				Yes - this was a missed SSI notification to the TGA. Sponsor justified that the existing Australian PI warnings for s47G(1)(a) were appropriate. However, the additions s47G(1)(a) differed and provided additional information compared to the existing wording in the Australian Product Information. The modifications were required to be notified to the TGA as an SSI.

Product	COR	High level description of request for safety-related action	Date of receipt to s22 organisation	Impact to compliance with SSI notification to the TGA?
s22				No, however the SSI assessment was required to have been completed and documented with the justification for not reporting. This was not done which represented non-compliance. An s47G(1)(a) had previously been submitted to the TGA for these safety issues, and the TGA was in the process of completing their review of s47G(1)(a)
				Yes - this was a missed SSI notification to the TGA. The Australian PI does not contain this warning/precaution topic.

Product	COR	High level description of request for safety-related action	Date of receipt to s22 s22 organisation	Impact to compliance with SSI notification to the TGA?
s22				Yes - this was a missed SSI notification to the TGA. Sponsor justified that the Australian PI already contained s47G(1)(a) . Therefore, no update to the Australian PI was warranted. However, the additions s47G(1)(a) differed and provided additional information compared to the existing wording in the Australian PI. The modifications were required to be notified to the TGA as an SSI.
				Yes - this was a missed SSI notification to the TGA. Sponsor justified that the Australian PI already contained s47G(1)(a) therefore no update to the Australian PI was warranted. However, the additions s47G(1)(a) differed and provided additional information compared to the existing wording in the Australian PI. Of note, there was s47G(1)(a) in the Australian PI. The modifications were required to be notified to the TGA as an SSI.

Product	COR	High level description of request for safety-related action	Date of receipt to s22 s22 organisation	Impact to compliance with SSI notification to the TGA?
s22				
				Yes - this was a missed SSI notification to the TGA. Sponsor justified that the Australian PI already highlighted s47G(1)(a) and contained warnings for s47G(1)(a) Whilst the warning regarding s47G(1)(a) was unchanged compared to the Australian PI, there were changes to the warning and precaution regarding s47G(1)(a) which included information additional to what was in the Australian PI. The modifications were required to be notified to the TGA as an SSI.

APPENDIX V: MAJOR DEFICIENCY 2.4

Current EU-RMP / EMA approval date	Date of sponsor receipt of current EMA approved EU-RMP	Examples of changes to safety concerns accepted by the EMA	TGA submission information
s22			Sponsor informed that there were no post-registration RMP submissions. The EU RMP submitted to the TGA with initial approval, s47G(1)(a)
			Sponsor informed that there were no post-registration RMP submissions. The EU RMP submitted to the TGA with initial approval, s47G(1)(a)
			Sponsor informed that there were no post-registration RMP submissions. The EU RMP submitted to the TGA with initial approval, s47G(1)(a)

APPENDIX VI: MAJOR DEFICIENCY 2.5

EU-RMP version / EMA approval date	Date of sponsor receipt of EMA approved EU-RMP	High level description of examples of changes to safety concerns approved by the EMA	Updated EU-RMP/ASA submission due date to the TGA (3 months post-EMA approval date)	TGA submission date (RMP/ASA version submitted to the TGA)	Delay (days)	Sponsor justification for delay
s22					1169	Evidence of the sponsor decision not to submit an updated RMP-ASA to the TGA for EU RMP s47G(1)(a) was not documented at the time. On s22, whilst discussing the s47G(1)(a) identified that the ASA required updating to reflect the current distribution practices. During the update of the ASA to s47G(1)(a) it was identified that there had been updates to the EU-RMP since the last version submitted that qualified for an updated RMP-ASA submission to the TGA. The updated ASA was submitted with the current EU-RMP s47G(1)(a)
					12 (EU-RMP) 321 (ASA)	EU RMP s47G(1)(a) was submitted to the TGA on s22 as part of the s47G(1)(a) In this updated EU-RMP that was submitted to the TGA, s47G(1)(a) When the ASA was next

EU-RMP version / EMA approval date	Date of sponsor receipt of EMA approved EU-RMP	High level description of examples of changes to safety concerns approved by the EMA	Updated EU-RMP/ASA submission due date to the TGA (3 months post-EMA approval date)	TGA submission date (RMP/ASA version submitted to the TGA)	Delay (days)	Sponsor justification for delay
s22						updated to s47G(1)(a), it was identified that this had not been reflected in the previously submitted ASA and the ASA was corrected in s47G(1)(a)
					623	Following sponsor receipt of EU-RMP s47G(1)(a) on s22, on s47G(1)(a) the s47G(1)(a) indicated that since that submission took place there have been other substantial changes to the list of safety concerns, starting with EU RMP s47G(1)(a) approved by EMA on s22 which were not submitted to the regulator. Confirmed to be a deviation on s22 and deviation was raised s47G(1)(a)

EU-RMP version / EMA approval date	Date of sponsor receipt of EMA approved EU-RMP	High level description of examples of changes to safety concerns approved by the EMA	Updated EU-RMP/ASA submission due date to the TGA (3 months post-EMA approval date)	TGA submission date (RMP/ASA version submitted to the TGA)	Delay (days)	Sponsor justification for delay
s22						
					355	
					223	
					487	During the impact analysis of deviation s47G(1)(a) , it was identified that the EU-RMP had been revised with updates to the classification of safety concerns, but this had not yet been submitted to the TGA RMP Coordinator.

EU-RMP version / EMA approval date	Date of sponsor receipt of EMA approved EU-RMP	High level description of examples of changes to safety concerns approved by the EMA	Updated EU-RMP/ASA submission due date to the TGA (3 months post-EMA approval date)	TGA submission date (RMP/ASA version submitted to the TGA)	Delay (days)	Sponsor justification for delay
s22						
					425	During the impact analysis of deviation s47G(1)(a) , it was identified that the EU-RMP had been revised with updates to the classification of safety concerns, but this had not yet been submitted to the TGA RMP Coordinator.
					342	During the impact analysis of deviation s47G(1)(a) , it was identified that the EU-RMP had been revised with updates to the classification of safety concerns, but this had not yet been submitted to the TGA RMP Coordinator.

EU-RMP version / EMA approval date	Date of sponsor receipt of EMA approved EU-RMP	High level description of examples of changes to safety concerns approved by the EMA	Updated EU-RMP/ASA submission due date to the TGA (3 months post-EMA approval date)	TGA submission date (RMP/ASA version submitted to the TGA)	Delay (days)	Sponsor justification for delay
		s22				

s22

s22

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22 ,

RE: TGA Pharmacovigilance Inspection of s22

Please find attached the inspection report for the remote pharmacovigilance inspection of s22 conducted by the Therapeutic Goods Administration (TGA) on s22 2023.

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*. The purpose of the inspection was to assess compliance with the relevant pharmacovigilance legislation and guidelines and the conditions specified in the relevant approvals for registration or listing on the Australian Register of Therapeutic Goods (ARTG), and any subsequent variations.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as Appendix I).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Commitment Tracker.

For certain deficiencies, including all major and critical deficiencies, you are requested to submit objective evidence of corrective or preventive actions after their completion dates.

Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed. In some circumstances, a re-inspection may be required to ensure completion of such activities.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Senior Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22 2023

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor address:	s22
Main site contact:	s22 and Australian Pharmacovigilance Contact Person
Inspection type:	Routine, systems-related inspection
Method of inspection:	Hybrid (Day 1 onsite, Day 2 & 3 remote)
Inspection scope:	To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines
Inspection date/s:	s22 2023
Inspector/s:	s22 (Lead), s22 (Co-inspector), s22 (Observer)
Inspection finding summary:	0 Critical Deficiencies 3 Major Deficiencies s22
Date report issued to sponsor:	s22 2023
Reference:	s22

Contents

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Introduction

s22 was selected for a routine inspection as part of the TGA's Pharmacovigilance Inspection Programme (PVIP); all acronyms used in this report are listed in Appendix III. The purpose of the inspection was to review compliance with currently applicable Australian pharmacovigilance (PV) regulations and guidelines. In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, effective January 2021 and v3.0, effective August 2023) (*Pharmacovigilance Guidelines*)
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

Company background:

s22 located in s22, was established in s22. The sponsors global headquarters are in s22, and the company was founded as a s22 . As of s22 is present in s22 with s22 staff across s22 There is s22 with s22 . In Australia, sponsored clinical trials have been undertaken since s22 and the s22 was registered on the ARTG on s22 remains the s22 sponsor product on the ARTG at the time of the inspection.

Since s22 the sponsor has s22 staff as of s22 Most staff are employed within s22 and other s22 within the sponsor organisation include s22 and s22 The roles of the Australian Pharmacovigilance Contact Person (A-PVCP) and Qualified Person for Pharmacovigilance in Australia (QPPVA) were fulfilled by different people. The current A-PVCP is a sponsor employee who also the s22 for Australia as defined in s22 Standard Operating Procedures (SOPs). The QPPVA role is fulfilled an employee of the s22 and the s22 There were s22 and most PV activities were delegated to the s22 team. s22 employees are predominantly located in s22 and s22

s47G(1)(a) is included in the Black Triangle Scheme (BTS) and has received approvals fo s47G(1)(a) Product registration for the s47G(1)(a) Post-approval, s47G(1)(a) has been supplied since s22 and s47G(1)(a) were supplied in Australia up to s22

s47G(1) company sponsored interventional clinical trials, s47G(1)(a) interventional investigator-initiated trial and s47G(1)(a) non-interventional investigator-initiated trial were ongoing at the time of the inspection. s47G(1)(a) s47G(1)(a) delivered by a vendor was ongoing and market research programs (MKR) and a s47G(1)(a) had been undertaken post-approval of s22 but were not ongoing.

Brief report of the inspection activities undertaken

Scope of inspection

The inspection was conducted onsite on Day 1 and thereafter, remotely via videoconference. The inspection included a review of both local and global PV systems. Company personnel from Australia, s22 attended the inspection via videoconference.

The inspection was conducted through interviews and review of documents, including searches of PV, Medical Information (MI) and product quality complaint (PQC) databases. The PV topic areas reviewed during the inspection are highlighted in the Inspection Plan (attached as Appendix II) and included a review of:

- the collection, management and reporting of spontaneous and solicited adverse reaction (AR) reports
- ongoing safety evaluation and the management of Significant Safety Issues (SSIs)
- the management of reference safety information (RSI)
- the management of PV post-approval commitments (PAC)
- the role of the A-PVCP and QPPVA
- the quality management system (QMS).

Documents submitted prior to the inspection

The company submitted an 'Australian Pharmacovigilance System Summary' (APSS) document on s22 s22 2023 to assist with inspection planning and preparation. Other specific documents including PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the company prior to the inspection.

Conduct of the inspection

The inspection was conducted in accordance with the Inspection Plan (attached as Appendix II).

Tabulated Summary of Inspection Deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing and reporting ARs and special situation reports received from spontaneous and solicited sources, were reviewed during the inspection. This included a review of all Australian reports received by the company between s22 . When required, the narrative and source documentation for specific cases were analysed. s22
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of company products were reviewed during the inspection. s22
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the inspection. Deficiencies related to the management and reporting of SSIs are described in Major Deficiency 3.
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the inspection. s22
Management of PAC	The procedure for managing PV PAC, including submission of Periodic Safety Update Reports (PSURs), maintenance of Risk Management Plan (RMP) documents and implementation of RMP commitments, was reviewed during the inspection. Deficiencies related to the management of PAC are described in Major Deficiency 1.
A-PVCP and QPPVA	During the inspection, the roles and responsibilities of the A-PVCP and QPPVA were reviewed including sponsor compliance with associated reporting obligations. Deficiencies in this topic are described in Major Deficiency 2.
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and SOPs, was reviewed during the inspection. s22

List of deficiencies identified during the inspection

Critical deficiencies

Nil critical deficiencies were identified during the inspection.

Major deficiencies

1. Deficiencies in management of PAC

1.1. Failure to submit updated RMP/Australian Specific Annex (ASA) following significant updates to the EU-RMP

In accordance with the *Guidelines on Risk management plans for medicines and biologicals, sponsors* **MUST** submit an updated RMP and/or ASA when we request it and **whenever there is significant change, such as: when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.**

For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the request of the TGA, then we recommended that the updated RMP/ASA is **submitted within 3 months of the change being accepted by the EMA.**

The sponsor failed to submit updated EU-RMPs and ASAs to the TGA following the European Medicines Agency (EMA) approval of changes to the summary of safety concerns.

At the time of the inspection, the current version of the RMP/ASA submitted to the TGA and accepted with the approval of s47G(1)(a) on s22, was the s47G(1)(a) A comparison of the summary of safety concerns in this RMP/ASA against the current EU-RMP at the time of the inspection s47G(1)(a) revealed significant differences that had not been notified to the TGA by the sponsor, including:

s47G(1)(a)

The update in the description of the important potential risk of s47G(1)(a) was a change within the current version of the EU-RMP. The other changes to the summary of safety concerns occurred in previous updates to the EU-RMP which indicated that there were multiple missed submissions to the TGA of an updated EU-RMP and ASA.

Sponsor staff in Australia were responsible for update of the ASA and submission to the TGA along with updated approved EU-RMPs. However, the sponsor acknowledged that it was during the preparation for the inspection they first became aware that updates to the EU-RMP had not been notified to the sponsor company by the s22

1.2. Failure to fulfil a regulatory request from the TGA for an updated RMP

> In accordance with the *Guidelines on Risk management plans for medicines and biologicals*, sponsors **MUST** submit an updated **RMP and/or ASA when we request it** and whenever there is significant change, such as: **when the summary of safety concerns changes**, including when the EMA has approved removal or reclassification of safety concerns.

A TGA request for an updated RMP and ASA from the sponsor was not fulfilled.

On s22 , the TGA RMP Coordinator s47G(1)(a) issued the following written request to the sponsor,

> s47G(1)(a)

The sponsor informed that this regulatory request was not tracked within the sponsors systems as a regulatory authority request for information.

Subsequently, the EU-RMP version s47G(1)(a) which included s47G(1)(a) was approved by the EMA with procedure s47G(1)(a) on s22 . Of note, the summary of safety concerns in the EU-RMP Version s47G(1)(a) differed from that presented in the s47G(1)(a) . For example, s47G(1)(

At the time of the inspection, almost two years after the EMA approval of EU-RMP s47G(1)(a) , no updated RMP had been provided to the TGA and the request s22 was not fulfilled.

1.3. Delay in fulfilment of a PAC

> In accordance with Subsection 28(2B) of *the Act*, the TGA may impose certain conditions of listing or registration on a therapeutic good when it is entered in the ARTG.

The TGA s47G(1)(a) letter dated s22 for s47G(1)(a) included a specific condition of registration that,

> s47G(1)(a)

PSUR s47G(1)(a) informed that s47G(1)(a)

However, at the time of the inspection the s47G(1)(a) had not been submitted to the TGA. Therefore, the s47G(1)(a) had been available for more than one year prior to submission to the TGA and the submission was also late in accordance with the specific timeline included in the condition of registration.

The sponsor provided the rationale:

> s47G(1)(a)

s47G(1)(a)

According to the global SOP, s47 However, during the inspection, no evidence was available to demonstrate sponsor escalation or decisions regarding this overdue commitment.

Furthermore, s47 The current sponsor oversight of compliance with safety related commitments, was determined to be ineffective based on this example.

1.4. Failure to implement targeted questionnaires as required in the RMP-ASA

> In accordance with subsection 28(2B) of the Therapeutics Goods Act 1989 and the conditions of registration, the approved Risk Management Plan, and any subsequent revisions, as agreed with the TGA **MUST** be implemented in Australia
>
> In accordance with the *Pharmacovigilance Guidelines*, you should follow up cases to obtain detailed supplementary information significant to the clinical evaluation of the cases. This is particularly important for monitored events of special interest (for example identified or potential risks and missing information in the Risk Management Plan.

During the inspection, delays with sponsor implementation of s22 , targeted questionnaires outlined in the ASA accepted by the TGA were identified.

The approval letter for the registration of s22 included the condition of registration:

s47G(1)(a)

However, the use of targeted follow-up questionnaires for s22 described in the ASA s22 as part of routine pharmacovigilance activities for s22 were not implemented s22 . This constituted a delay of s22 , since the implementation was required from the time of approval.

The sponsor became aware of this non-compliance and created an associated quality event in their s22 on s22 . Consequently, on s22 implemented the use of the three targeted questionnaires within the case workflow. The CAPA Plan for this deviation also included the development and implementation of a work instruction (s47G(1)(a) to ensure future questionnaires would be implemented s47G(1)(a) and the retrospective identification and sending of the questionnaires for the relevant cases.

1.5. Deficiencies in company procedures to outline responsibilities for maintenance of the ASA

In accordance with the *Guidelines on Risk management plans for medicines and biologicals*, you should update your risk management plan when new information becomes available regardless of whether your product is marketed. **You should ensure that you always keep your RMP and ASA up to date for your own records and because we may request an updated RMP from you at any time.**

Sponsors **MUST** submit an updated RMP and/or ASA when we request it and whenever there is significant change, such as: when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.

For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the request of the TGA, then we recommended that the updated RMP/ASA is submitted **within 3 months of the change being accepted by the EMA.**

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

During the inspection discrepancies in the process followed compared to the process documented in company procedures were identified in relation to maintenance of the ASA.

During the inspection interview the sponsor described that s47G(1)(a) was responsible to author, maintain and submit the ASA to the TGA and that s47G(1)(a) had a role to review the drafted ASA. There was no local procedure to define roles, responsibilities, requirements and timelines towards the ongoing maintenance of the ASA and the sponsor informed that the relevant procedure was global SOP, s47 . However, except for submission of the ASA to the health authority, s47 did not align with the verbally described process. For example, s47 defined that:

s47

In addition, both versions of the s47 and the subsequent s47 outlined that s22 was responsible to prepare RMPs. Specific responsibilities towards local RMPs were not specified.

The sponsor is responsible for compliance with the TGA *Guidelines on Risk management plans for medicines and biologicals* and should develop clear written SOPs to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

1.6. Deficiencies in the procedure for oversight/tracking and fulfilment of all PACs

In accordance with Subsection 28(2B) of the Act the TGA may impose certain conditions of listing or registration on a therapeutic good when it is entered in the ARTG.

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

The sponsor did not track the following conditions of registration for s22 as PAC in the designated company tracking system for post approval commitments, s47G(1)(a) system:

- Inclusion for the designated period in the BTS
- Notification to the TGA of commencement of supply
- Implementation of the RMP-ASA and subsequent revisions

The following was noted from a review of the responsibilities outlined in the current s47

s47

There was no company procedure that otherwise described roles and responsibilities towards the BTS nor the notification to the TGA of commencement of supply. Consequently, because not all safety-related commitments for s22 were tracked in line with s47 it was not clear how compliance could be monitored.

Deficiencies in company processes regarding maintenance of the RMP-ASA and submission to the TGA of subsequent revisions are discussed further in the previous deficiencies.

2. Deficiencies in the role of the A-PVCP and QPPVA

2.1. Deficiencies in access to PV data

In accordance with the *Pharmacovigilance Guidelines*, the pharmacovigilance data collected, collated and electronically stored **MUST** be available from a single access point within Australia.

During the inspection, it was revealed that the sponsor did not have access to the Australian PV data from a single access point in Australia from s22 .

The sponsor confirmed that, prior to the engagement of the s22 who is based in Australia, there was no previous sponsor employee in Australia who had access to Australian cases in the global safety database (GSD), the repository where the Australian PV data was electronically stored. s22 access to the GSD was granted on s22 to perform her role. No second person in Australia had access and there was no contingency for access from a single access point within Australia, if s22 was absent.

It was noted that the job description (JD) for the current A-PVCP signed on s22 outlined responsibility for PV oversight which included s47G(1)(a) however the A-PVCP did not have direct access to the GSD. Instead, the A-PVCP access to PV data was facilitated through s47G(1)(a) through an online ticketing system managed by the s47G(1)(a) team.

2.2. Deficiencies in the appointment of a QPPVA and a back-up QPPVA

> In accordance with the *Pharmacovigilance Guidelines*, you should have a qualified person responsible for pharmacovigilance undertakings in Australia (…) The Qualified person responsible for pharmacovigilance in Australia (QPPVA) should ensure that the sponsor has an effective pharmacovigilance system in place and complies with the legal pharmacovigilance requirements.
>
> We recommend the QPPVA:
> • lives in Australia
> • is permanently and continuously available (or at least within the hours of 9am-5pm AEST Monday to Friday), with a back-up person nominated should the primary QPPVA be absent
> • is trained and experienced in pharmacovigilance and relevant legislation in Australia
>
> The QPPVA needs to have adequate understanding of the Australian and global pharmacovigilance processes in order to allow them to have effective oversight of the entire pharmacovigilance system.

Prior to the TGA notification to the sponsor on s22 of the PV inspection, the sponsor did not appoint any QPPVA nor back up-QPPVA. Furthermore, it could not be verified that the QPPVA and back-up QPPVA appointed at the time of the inspection had an adequate understanding of the Australian PV processes due to their s47G(1) recency of appointment to the roles and absence of prior experience in relevant (PV) legislation in Australia.

The TGA inspection notification letter included a request for the A-PVCP to, "*Please ensure this notification is forwarded to the qualified person responsible for pharmacovigilance in Australia*." The appointment of the first and current QPPVA subsequently occurred on s22 . The sponsors first medicine was registered on the ARTG on s22 ; therefore, the sponsor did not have a QPPVA for a period of more than s22 .

The lack of appointment of a QPPVA trained and experienced in PV and relevant legislation in Australia and with an understanding of the Australian and global PV processes prior to s22 is likely to have contributed to some of the deficiencies identified in the inspection. The QPPVA is responsible to ensure that an effective PV system in place, compliant with the legal PV requirements.

It is acknowledged that upon awareness, the sponsor acted quickly to appoint a QPPVA s47G(1)(a) Specific training on Australian PV requirements was undertaken after his appointment to the role of QPPVA on s22 and s22 . However, the QPPVA did not have any prior experience in relevant (PV) legislation in Australia and this experience was not required according to his JD s22

The first sponsor back-up QPPVA was appointed with a delay, on s22 . Whilst this responsibility was included in the individuals Curriculum Vitae from s22 , this responsibility was not reflected in the current JD provided to the TGA on s22

The QPPVA and back-up QPPVA were located in s22 . It was not clear therefore that the TGA recommendation to be permanently and continuously available s22 could be met.

2.3. Deficiencies in sponsor procedures related to the role of the A-PVCP

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

Specific elements of the sponsors reporting obligations (responsibilities and timelines) towards the A-PVCP as specified in the *Pharmacovigilance Guidelines* were not adequately described in sponsor procedures. For example, there was no description regarding:

- recommendation to regularly check your TGA Business Services (TBS) profile to ensure the Australian pharmacovigilance contact person's details remain correct
- requirement to provide the TGA with the name and contact details of the A-PVCP within 15 calendar days of the sponsors first medicine's entry on the ARTG
- requirement to notify the TGA of the updated name and contact details within 15 calendar days of any changes to the A-PVCP or their details.

The sponsor did not retain records of changes to the appointed A-PVCP in TBS, including what changed and the date of the change.

It is acknowledged that no non-compliance with the sponsors notification to the TGA of the A-PVCP in TBS was identified during the inspection.

The JD for the prior A-PVCP appointed from s22 , did not outline any responsibilities towards PV nor their responsibility to fulfil the role of the A-PVCP.

The sponsors appointed A-PVCP was also appointed to the company role of s47G(1)(a) defined as

s47G(1)(a)

Prior to the implementation of the s47G(1)(a) the sponsor informed that there was no formal documented delegation of sponsor PV responsibilities from the appointed s47G(1)(a), despite PV responsibilities mostly being centralised to s47G(1)(a) via verbal delegation during this time.

The responsibility for creation of this matrix first came into effect on s22 with s47, however the matrix was implemented with a delay for Australia, more than 8 months after s47 was in effect and of note, after the TGA notification of the inspection.

3. Deficiencies in the management of SSIs

3.1. Failure to identify and notify an SSI to the TGA

> In accordance with the *Pharmacovigilance Guidelines*, (version 2.2 effective January 2021 to July 2023), an example of a significant safety issue includes safety-related actions by comparable international regulatory agencies such as (…) the addition or modification, for safety reasons, of a warning or precaution statement to the product information or label.
>
> Sponsors **MUST** report all significant safety issues related to their medicine to the TGA within 72 hours.
>
> A safety issue leading to international regulatory action is considered to be significant and hence reportable regardless of whether you agree with the recommendations and conclusions of the international regulator.

A review of safety issues managed by the sponsor during the inspection sample period, s22 revealed that a safety related request from th s47G(1)(a) was not identified to be an SSI, not notified to the TGA and the sponsor justification for not reporting was not aligned to the TGA requirements.

Evidence of a specific SSI assessment from the time of management of this safety issue was not available. The sponsor provided the following SSI assessment and justification for not reporting this safety issue as an SSI to the TGA in response to an inspection request:

> s47G(1)(a)

This justification did not align with the *Pharmacovigilance Guidelines.* s22 are a comparable overseas regulator (COR) and in accordance with version 2.2 of the *Pharmacovigilance Guidelines* which was effective at the time of company management of this request, a request from a COR for the addition of a warning or precaution statement to the PI for safety reasons was a specific example of an SSI. The *Pharmacovigilance Guidelines* also stated that a safety issue leading to international regulatory action is significant and hence reportable regardless of whether the sponsor agreed with the recommendations and conclusions of the international regulator.

s22 requested the addition s22 to the label as a warning and precaution on s22 It is acknowledged that the Australian PI was updated to include this warning and precaution in the latest revision of the PI s22 Therefore, there was no impact to patients or public health because of the non-

reporting of the SSI. This did not however negate the sponsors responsibility to notify the TGA of this SSI and it was noted that the justification for non-reporting of this safety issue as an SSI did not include this Australian specific context regarding the Australian PI under assessment.

3.2. Failure to incorporate SSI definition and requirements into company procedures

In accordance with the *Pharmacovigilance Guidelines* s22 , a significant safety issue is a new safety issue or validated signal considered by you in relation to your medicines that requires urgent attention of the TGA.

Examples of significant safety issues include safety-related actions by comparable international regulatory agencies such as
– the withdrawal or suspension of the medicine's availability
– the addition or modification, for safety reasons, of a contraindication, warning or precaution statement to the product information or label
– the modification or removal, for safety reasons, of an indication.
(please refer to the Guidelines for the full list of examples)

A safety issue leading to international regulatory action is considered to be significant and hence reportable regardless of whether you agree with the recommendations and conclusions of the international regulator.

If you determine after appropriate assessment that a safety issue is not significant and do not report it, you should document a justification for this decision. We may ask you to provide this documentation at any time. If in doubt about a safety issue, treat it as significant (or contact us for advice).

Sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

Where you have a global parent company, you need to be confident that your SOPs will ensure you become aware of international safety information and regulatory actions in a timely manner.

During the inspection it was confirmed that no company SOP (global or local) included the TGA definition of an SSI. Company procedures were based on EU Good Pharmacovigilance Practice (GVP) Module 9 and cited the definition of an Emerging Safety Issue (ESI). The TGA definition of an SSI does not fully align with the ESI definition, however.

Additionally, company procedures did not outline responsibilities and timelines to ensure that the following TGA requirements and recommendations were met:

- SSI assessment of validated signals
- Timely notification to the sponsor company in Australia of safety related actions by CORs for notification to the TGA as an SSI (as applicable)
- Documentation of the justification for the decision that a safety issue is not significant not reportable to the TGA as an SSI
- 72-hour reporting of an SSI upon receipt to the sponsor.

The sponsor informed that the assessment of s47G(1)(a) against the TGA SSI definition was completed by s47G(1)(a) . The assessment date was the date of the applicable s47G(1)(a) (indicated in the s47G(1)(a) . The s47G(1)(a) took place following s47G(1)(a) however, whereas

Version 2.2 of the *Pharmacovigilance Guidelines (version 2.2 effective January 2021 to 31 July 2023)*, described that *"a significant safety issue is a new safety issue or **validated** signal*" not an assessed signal. Prior to 01 August 2023 and the publication of version 3.0 the *Pharmacovigilance Guidelines*, the SSI assessment was required to occur at an earlier time point in the sponsors signal management process than at s47G(1)(a) . Additionally, a sample of s47G(1)(a) from the inspection sample period were reviewed s47G(1)(a) and no assessment of the safety issue against the TGA SSI definition was documented in the minutes.

In another example, described in Major Deficiency 3.1, no documented SSI assessment from the time of management of the safety related request from s22 to the warning and precaution section of the s47G(1)(a) PI, was available.

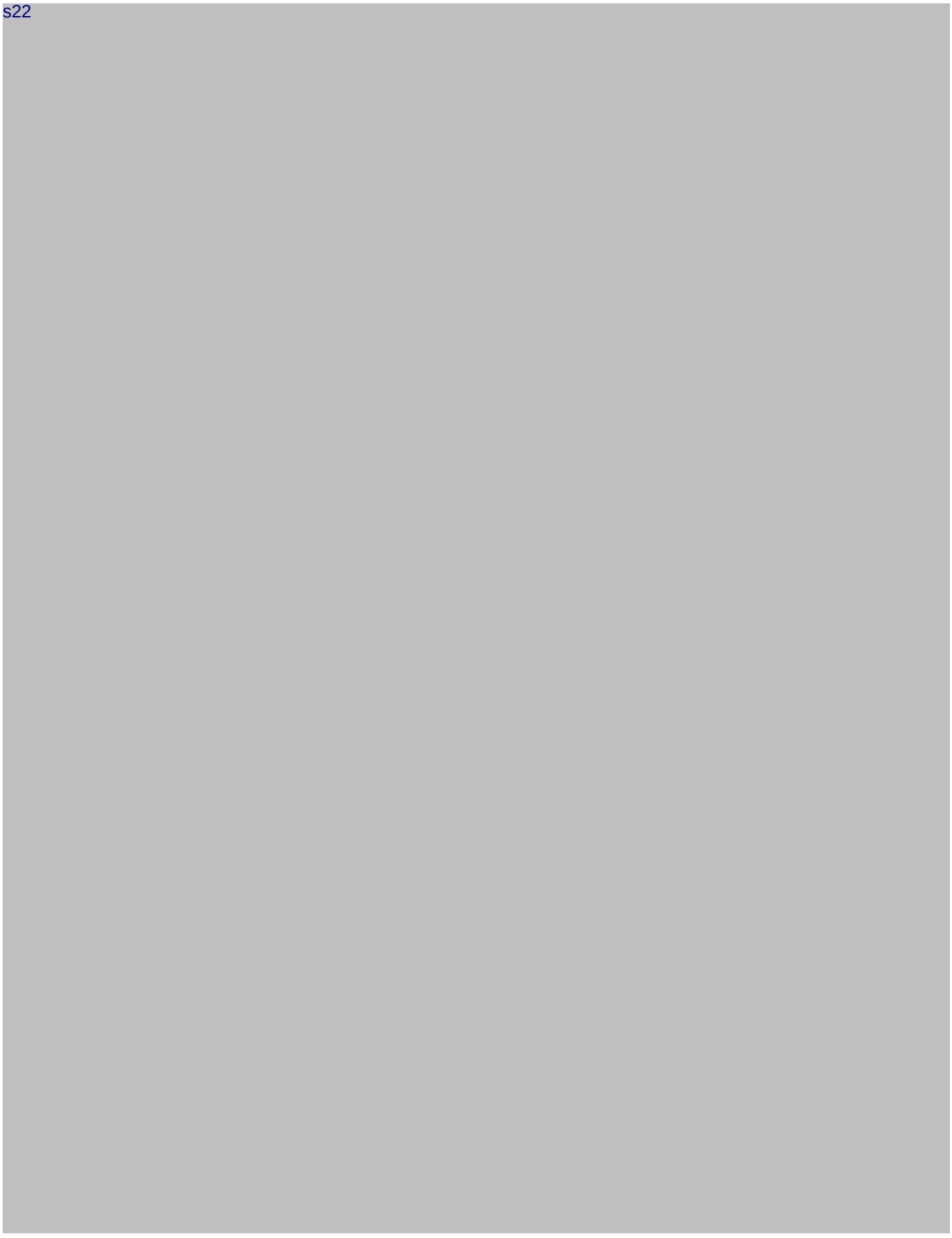
It was informed in the inspection interview that s47G(1)(a) had awareness of the TGA requirements for SSIs, however this could not be verified as the company procedures and the available evidence of management of safety issues did not reflect the TGA requirements.

Whilst the inspection revealed one example of a missed SSI notification to the TGA, the lack of evidence of incorporation into the sponsor PV system of the mandatory reporting obligations and TGA recommendations towards SSIs created the potential for other missed or delayed notifications. Given the seriousness and potential major impact on the benefit-risk balance of the medicine and/or on patient or public health of SSIs which could warrant prompt regulatory action and/or communication to patients and healthcare professionals, a major grading was assigned to this deficiency.

s22

s22

s22



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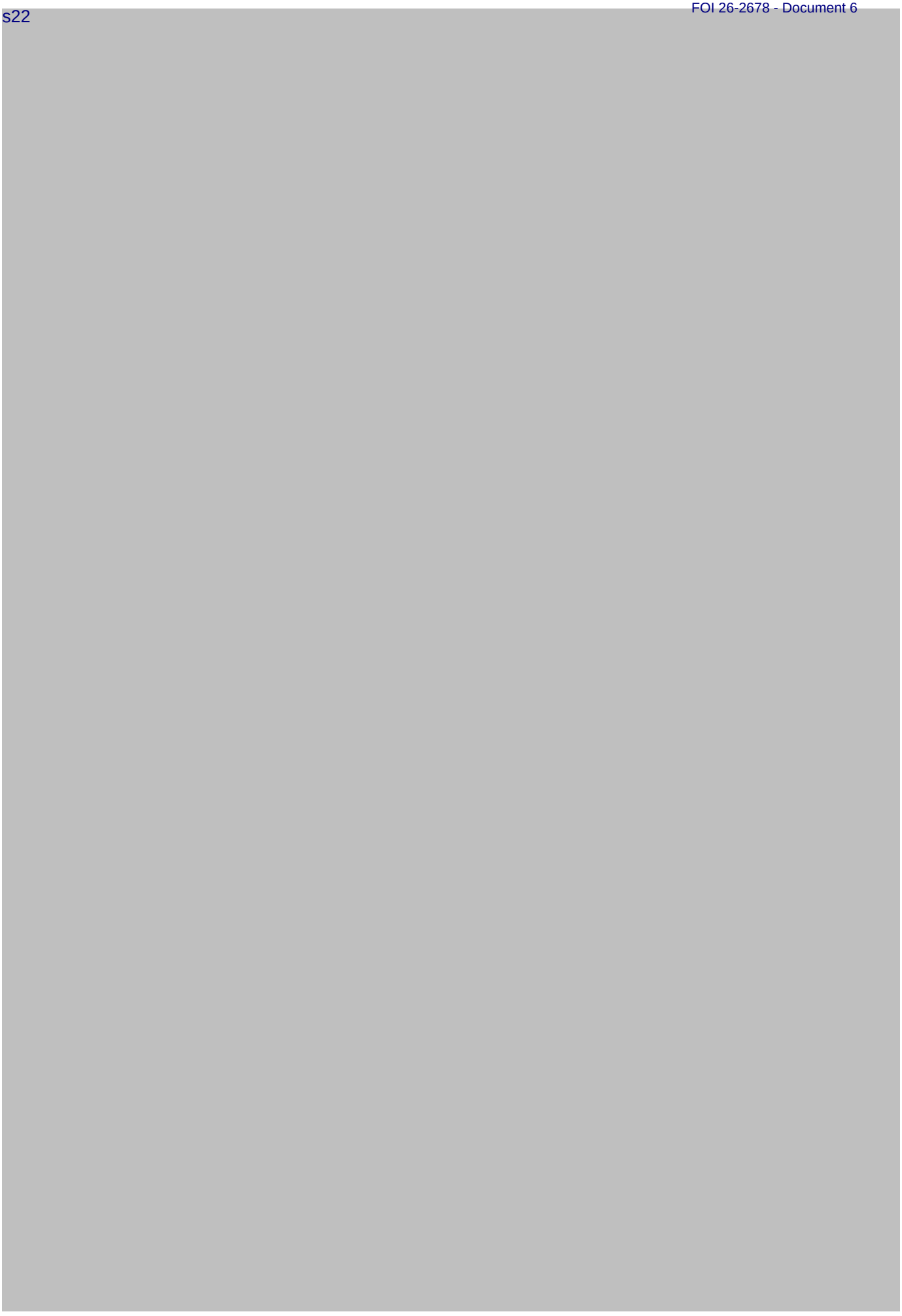

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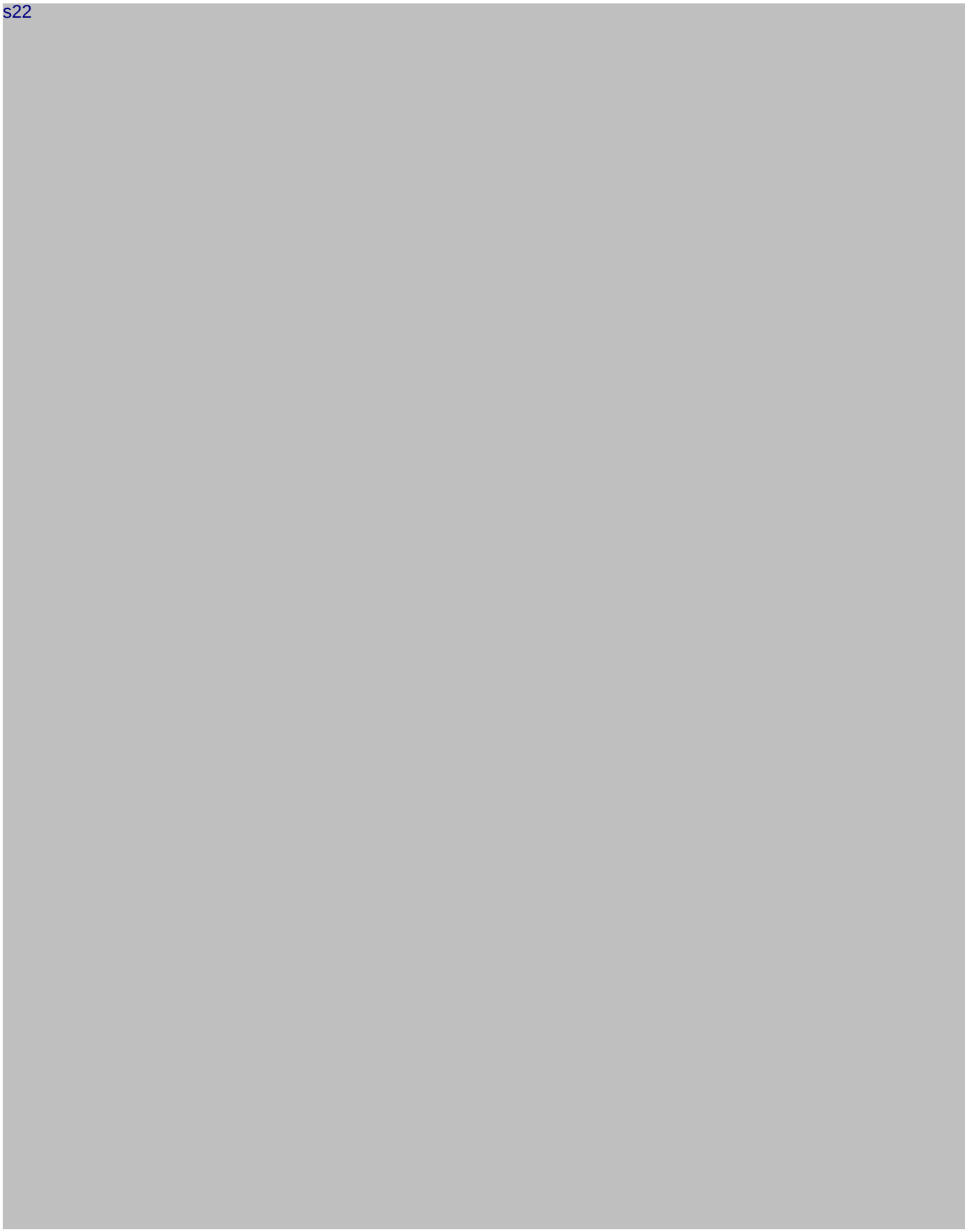

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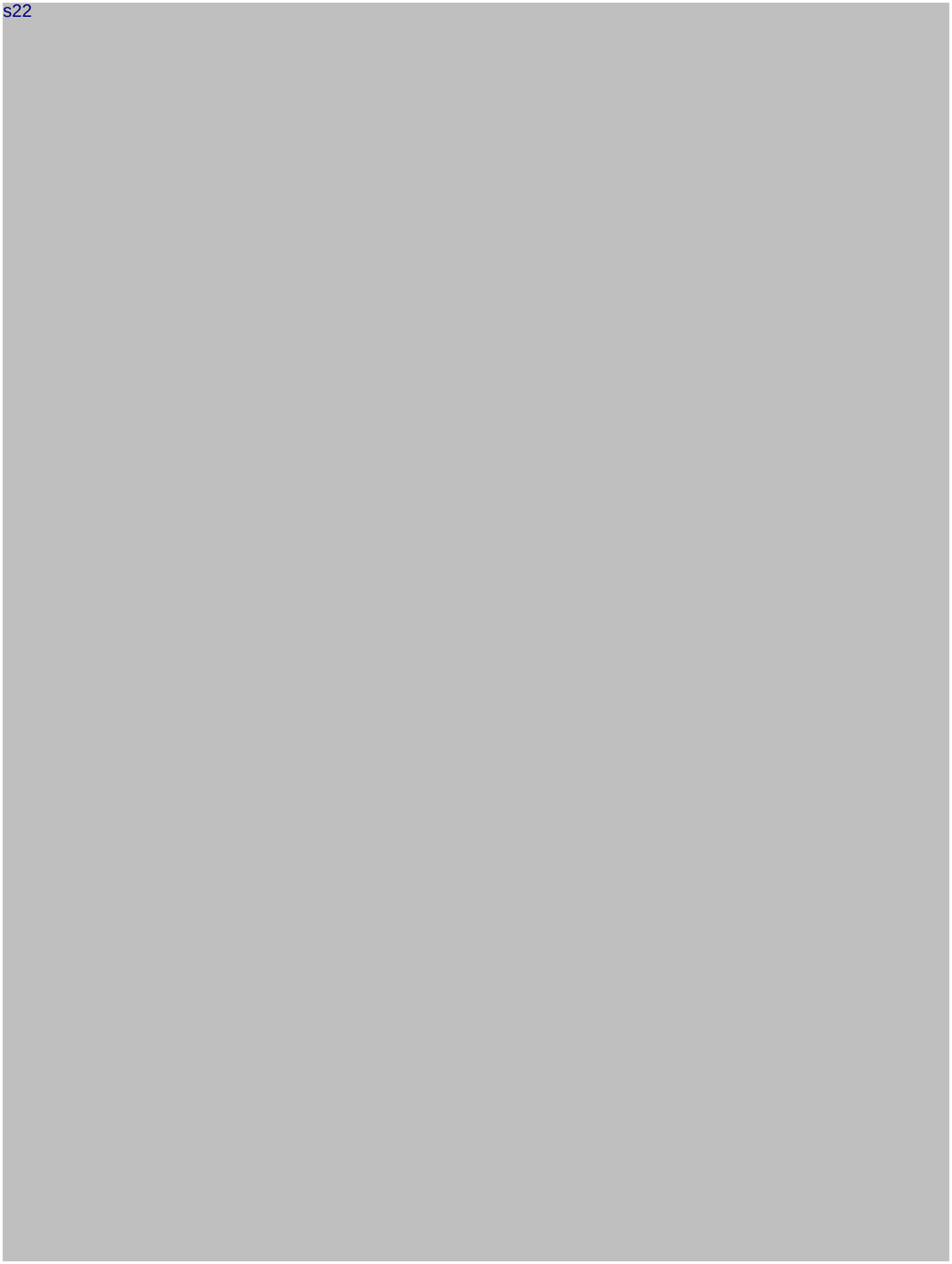

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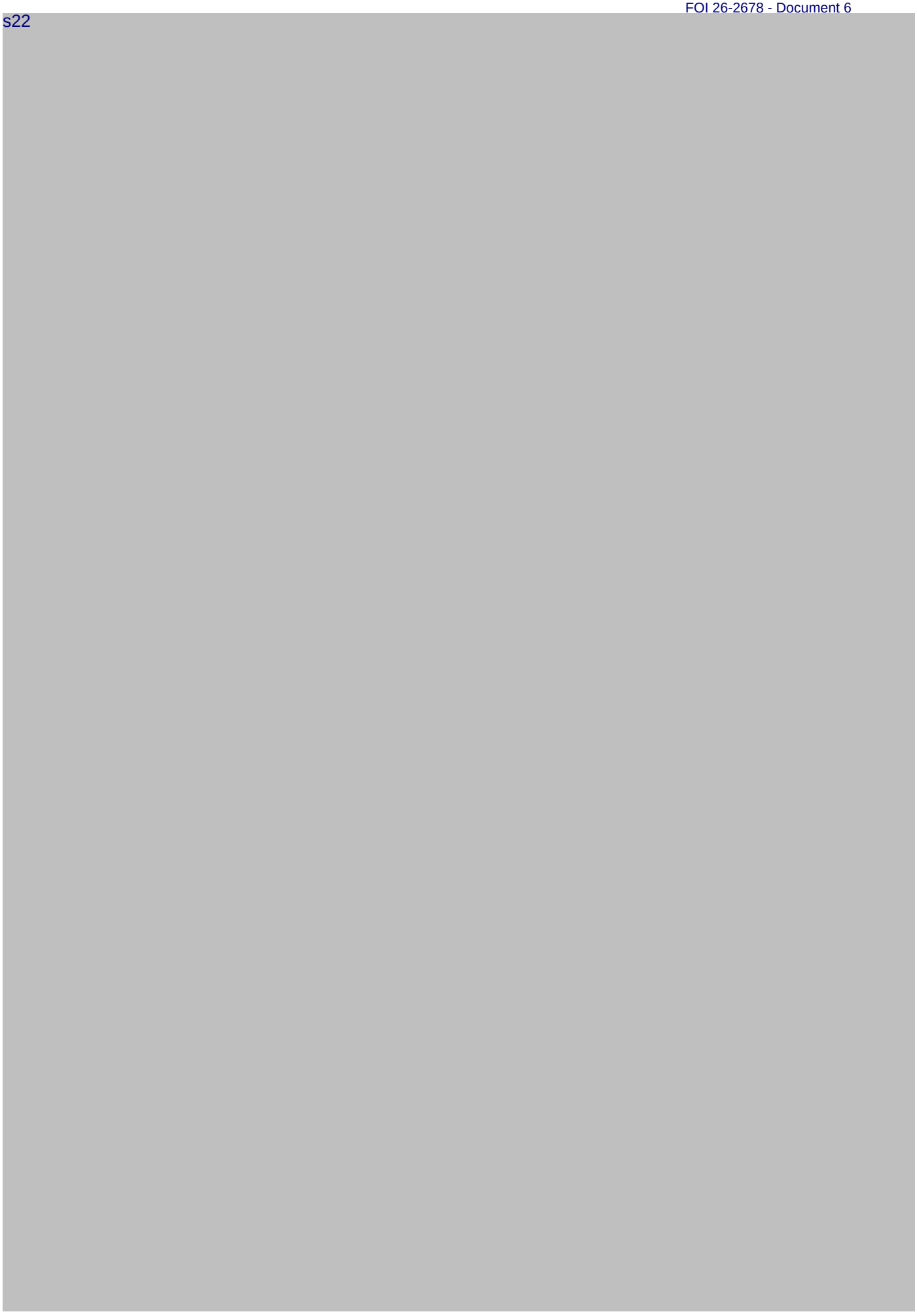

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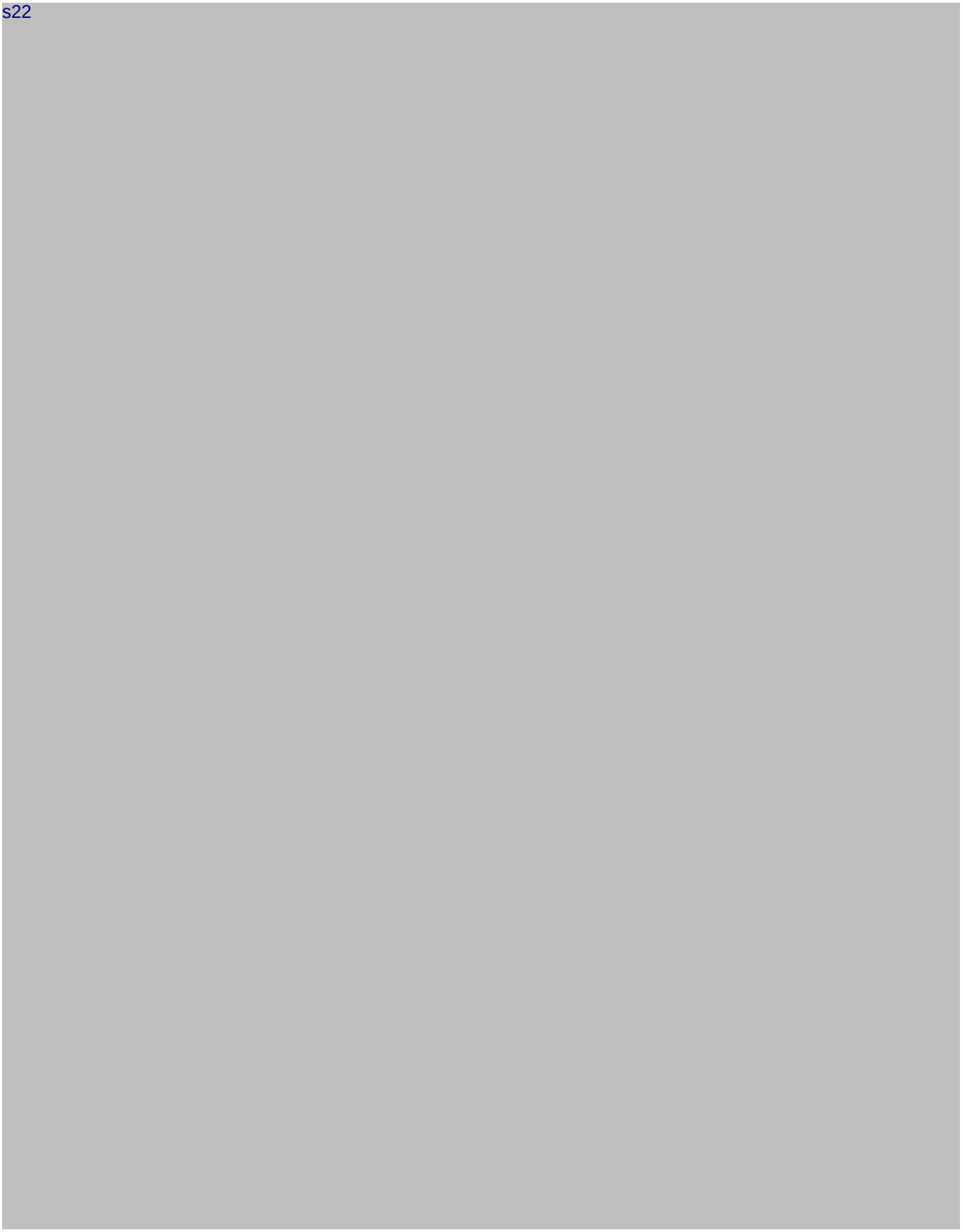

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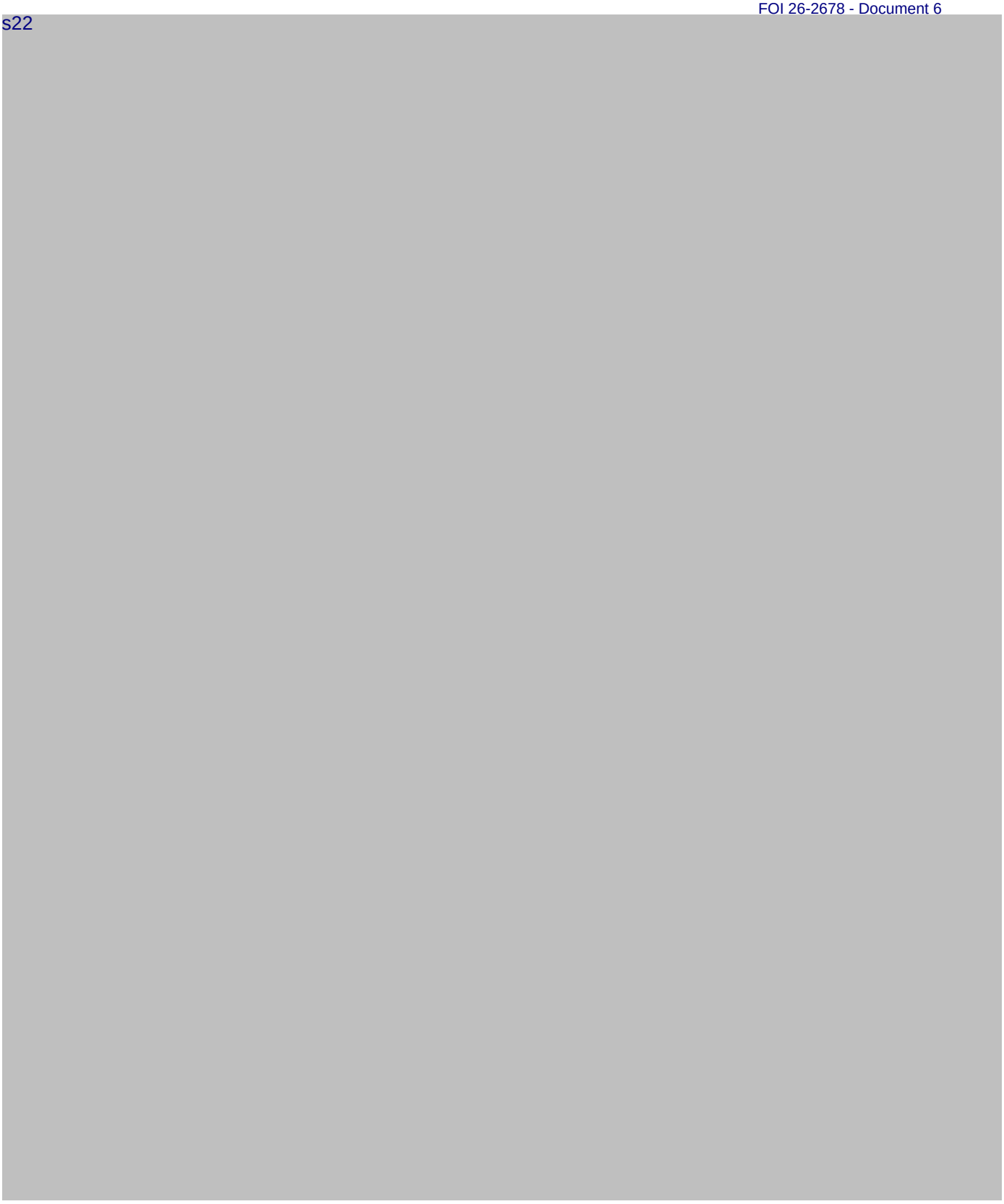

APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Pharmacovigilance Inspection Plan

Sponsor name:	s22
Sponsor address:	s22
Inspection type:	Hybrid (Day 1 onsite, Day 2 & 3 remote)
Inspection dates:	s22 2023
Inspectors:	s22 (lead inspector), s22 (co-inspector), s22 (observer)

Time (AEDT)	Activity	Staff involved
	PRE-INSPECTION CALL s22 *2023*	
10 – 11am AEDT s22	*Pre-inspection meeting* • Inspection logistics • Testing audio, video, screen sharing • Q&A	*TGA* s22 *Sponsor Staff* s22
	DAY 1 - Onsite s22 *2023*	
9:30 – 10.45am AEDT s22	*Opening meeting* • Introductions • Attendance • Scope • Confirmation of Inspection Plan	*TGA* s22 *Sponsor Staff* s22
	Company Presentation Overview of the company and pharmacovigilance system (~20 mins)	

Time (AEDT)	Activity	Staff involved
s22	**Tour of the office** (~15 mins)	s22
	Break	
11am – 12.30pm AEDT s22	**Case collection** • Spontaneous sources of data • Solicited sources of data	*TGA* s22 *Sponsor Staff* s22

Time (AEDT)	Activity	Staff involved
		s22
12.30 – 1.30pm	**Lunch/Break**	
1.30 – 3pm AEDT s22	**Review of procedures for the management of:** • Case entry • Case management • Follow-up • Quality assurance **Expedited reporting of adverse drug reactions to the TGA**	*TGA* s22 *Sponsor Staff* s22
3 - 3.30pm	**Break**	
3.30 - 4.30pm AEDT s22	**Maintenance of Reference Safety Information** • Process for updating PI and CMI following the identification of new safety information (Sponsor and TGA initiated) • Implementation of PI and CMI following approval	s22 *Sponsor Staff* s22

Time (AEDT)	Activity	Staff involved
s22		s22
	DAY 2 - Remote s22 *2023*	
8.30 – 10.00am AEDT s22	**Ongoing monitoring and signal management** **Management and reporting of significant safety issues to the TGA**	*TGA* s22 *Sponsor Staff* s22

Time (AEDT)	Activity	Staff involved
		s22
10 – 10.30am	**Break**	
10.30am-12pm AEDT s22	**Post-approval pharmacovigilance commitments** • Conditions of registration • RMPs • PSURs	s22 *Sponsor Staff* s22
12 – 1pm	**Lunch/Break**	
1 - 2.30pm AEDT	**Document reviews and ad-hoc interviews if required**	

Time (AEDT)	Activity	Staff involved
s22	**Quality Management Systems** • SOPs • Pharmacovigilance training • Record retention timelines • Pharmacovigilance audits **Role and responsibilities of the A-PVCP and QPPV-A**	*TGA* s22 *Sponsor Staff* s22
	DAY 3 - Remote s22 *2023*	
10am AEDT	**Cut-off for document delivery for the closing meeting**	
4pm AEDT s22	**Closing meeting**	*TGA* s22

Time (AEDT)	Activity	Staff involved
s22		*Sponsor Staff* s22

The times indicated are for guidance only and can be modified to suit

Ad hoc sessions to be included if required throughout the inspection

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
APSS	Australian Pharmacovigilance System Summary
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
BTS	Black Triangle Scheme
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
s47G(1)(a)	
CMI	Consumer Medicine Information
COR	Comparable Overseas Regulator
s47G(1)(a)	
EMA	European Medicines Agency
ESI	Emerging Safety Issue
EU	European Union
s47G(1)(a)	
GPS	Global Patient Safety
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
JD	Job Description
s47G(1)(a)	
MKR	Market Research program(s)
MSA	Master Services Agreement
s47G(1)(a)	
PAC	Post-approval commitment(s)
PI	Product Information
PQC	Product Quality Complaint
PSUR	Periodic Safety Update Report
PT	Preferred Term (MedDRA)
PV	Pharmacovigilance
PVIP	Pharmacovigilance Inspection Program
QMS	Quality Management System
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
s47G(1)(a)	
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
s47G(1)(a)	
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
TBS	TGA Business Services
TGA	Therapeutic Goods Administration
s47G(1)(a)	
USA	United States of America

s47G(1)(a)

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22

RE: TGA Pharmacovigilance Inspection of s22

Please find attached the inspection report for the remote pharmacovigilance inspection of s22 conducted by the Therapeutic Goods Administration (TGA) on s22 s22 2023.

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*. The purpose of the inspection was to assess compliance with the relevant pharmacovigilance legislation and guidelines and the conditions specified in the relevant approvals for registration or listing on the Australian Register of Therapeutic Goods (ARTG), and any subsequent variations.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as **Appendix I**).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Commitment Tracker.

For certain deficiencies, you may be requested to submit objective evidence of corrective or preventive actions after their completion dates.

Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed. In some circumstances, a re-inspection may be required to ensure completion of such activities.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Lead Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22 2024

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor address:	s22
Main site contact:	s22 Australian Pharmacovigilance Contact Person/QPPVA
Inspection type:	Routine / System based
Method of inspection:	Remote
Inspection scope:	To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines
Inspection date/s:	s22 2023
Inspectors:	s22 (Lead), s22 (co-inspector), s22 (co-inspector)
Inspection finding summary:	1 Critical Deficiency 1 Major Deficiency s22
Date report issued to sponsor:	s22
Reference:	E23-279323

Contents

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Introduction

s22 was selected for a routine inspection as part of the TGA's Pharmacovigilance Inspection Programme (PVIP); all acronyms used in this report are listed in **Appendix III**. The purpose of the inspection was to review compliance with currently applicable Australian pharmacovigilance (PV) regulations and guidelines. In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021 and v3.0, effective August 2023) (*Pharmacovigilance Guidelines*)
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

Company background:

s22 (sponsor) is a fully owned s22 . Prior to the s22 was a s22 owned company. s22 is a global s22 company based in s22 and is involved in the s22 is comprised of s22 members. There is no dedicated PV staff within s22 as the s22 functions are performed by s22 safety team. s22 relied on the s22 team to support PV activities within Australia. The current Australian Pharmacovigilance Contact Person (APVCP) and Qualified Person for Pharmacovigilance in Australia (QPPVA) is fulfilled by the s22 as defined in s22 standard operating procedure (SOP). s22 SOP also outlined the roles and responsibilities undertaken by the s22 and referred to s22 local and global SOP for PV activities. Most PV activities were delegated to s22 with the QPPVA providing oversight.

PV activities performed by s22 team include:

- PV training
- assessment of significant safety issues (SSI)
- reconciliation with internal and external stakeholders
- preparation and maintenance of local PV written procedures.

PV activities outsourced to s22 include:

- medical information (MI)
- case collection and processing
- follow up activities
- global and local literature search/review

PV activities performed by s22 team include:

- maintenance of global safety database (GDS)
- signal detection and management
- regulatory surveillance
- quality management system

s22 is the sponsor of s22 entries on the Australian Register of Therapeutic Goods (ARTG) and at the time of the inspection, s22 products s22 were being supplied in Australia:

s22

No post-registration studies or programs involving the products have been initiated by the sponsor to date.

Brief report of the inspection activities undertaken

Scope of inspection

The inspection was conducted remotely via videoconference and included a review of both local and global PV systems. Company personnel from Australia, s22 attended the inspection via videoconference.

The inspection was conducted through interviews and review of documents (including searches of PV, MI and product quality complaint (PQC) spreadsheets). The PV topic areas reviewed during the inspection are highlighted in the pharmacovigilance inspection plan (attached as **Appendix II**) and included a review of:

- the collection, processing and reporting of spontaneous adverse reaction (AR) reports
- ongoing safety evaluation and the management of SSIs
- the management of reference safety information (RSI)
- the management of PV post-approval commitments (PAC)
- the role of the APVCP and QPPVA
- the quality management system (QMS)

Documents submitted prior to the inspection

The company submitted an 'Australian Pharmacovigilance System Summary' (APSS) document on s22 s22 to assist with inspection planning and preparation. Other specific documents including PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the company prior to the inspection.

Conduct of the inspection

In general, the inspection was conducted in accordance with the inspection plan (attached as **Appendix II**).

Tabulated Summary of Inspection Deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing, and reporting ARs and special situation reports received from spontaneous sources, were reviewed during the inspection. This included a review of a sample of Australian reports received by the company between s22 When required, the narrative and source documentation for specific cases were analysed. s22
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of company products were reviewed during the inspection.

	s22 [redacted]
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the inspection. Deficiencies related to the management and reporting of SSIs are described in Major Deficiency 1.
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the inspection. Deficiencies related to the management of Australian RSI are described in Critical Deficiency 1.
PAC	The procedure for managing PV PAC, including notification of commencement of supply, was reviewed during the inspection. s22 [redacted]
Role of the APVCP and QPPVA	During the inspection, the roles and responsibilities of the APVCA and QPPVA were reviewed. s22 [redacted]
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and SOPs, was reviewed during the inspection. s22 [redacted]

List of deficiencies identified during the inspection

Critical deficiency

1. Deficiencies in the Management of RSI

1.1. *Delays in updating generic PIs to align with innovator PI*

In accordance with the specific condition of registration for generic products, sponsors MUST update PI and CMI documents within one month of safety-related changes made by the innovator.

The *Pharmacovigilance obligations of medicine sponsors - frequently asked questions* state, if you are a sponsor of a generic medicine, it is a condition of registration that you make a submission to the TGA, to align the PI document of your generic product with the Australian innovator PI document, within one month of the date of approval of the safety-related update to the Australian innovator PI document. This is to ensure that safety-related information is consistent in all Australian products containing the same active ingredient, for quality use of medicines by patients and healthcare professionals.

According to the *Pharmacovigilance Guidelines*, where you have a global parent company, you need to be confident that your SOPs will ensure you become aware of international safety information and regulatory actions in a timely manner.

All safety-related variations submitted to the TGA by the sponsor to align the generic PI with the innovator PI between s22 were submitted with a delay. s22 eight examples of delayed submissions were identified, and delays ranged from 3 days to more than eight months. The most recent submission s22 was made on s22 s22 with a delay of more than 3 months.

Since the sponsor did not maintain the PI for products that were not marketed in Australia, this non-compliance was based on a review of variations submitted to the TGA for all sponsor generic medicines marketed during the sampling period. Information regarding the eight examples of non-compliance is outlined in Appendix IV.

The sponsor informed that the products in all these examples were currently supplied in Australia at the time of the inspection and that between s22, the supply volume was as follows:

s22

Additionally, safety-related PI updates were significant and included additional warnings and precautions, additional interactions and additional adverse reactions. Therefore, the evidence demonstrated that the delayed update of RSI for these products presented a serious violation of applicable legislation and guidelines. It is necessary that all PIs available to healthcare professionals and patients are kept up-to-date to ensure the safe use of medicine.

A review of sponsor procedures for the management of safety updates to Australian PI, effective during the period of the above examples, revealed that the process was not aligned with the specific

condition of registration for generic products, included in the approval letters for s22 [redacted]

Furthermore, information regarding generic PIs alignment with innovator, including timeline, was included in the *TGA Pharmacovigilance Frequently Asked Question*, which was published on the TGA website in January 2021. Refer to Critical Deficiency 1.6 for further discussion regarding sponsor RSI procedures. The sponsor informed that the reason for the delayed submission of the safety variation for s22 [redacted], referenced in Appendix IV, was an insufficiently specified timeline for submission in sponsor procedure, s47 [redacted]

It was also noted that the updates to the s22 [redacted] were aligned with the safety-related request from the s22 [redacted] which the s22 [redacted] was aware of from s22 [redacted], 9 months and 20 days prior to the submission of the s22 [redacted] to the TGA. The s22 [redacted] updated the s22 [redacted] which was approved on s22 [redacted] but this was not communicated to the sponsor.

1.2. Delays in lodging the PIs on the TGA website (after TGA approval)

In accordance with the Conditions of registration, sponsors **MUST** lodge any necessary updates to the PI within 2 weeks of the date of TGA approval.

The PI **MUST** be lodged in the TGA eBusiness Services system.

Delays in the lodgement of the updated PI on the TGA website were identified following the TGA approval of two safety related requests (SRR) in s22 [redacted]. Further details are provided in the table below.

Product (Trade names)	Submission No.	Date of TGA approval	Date of sponsor upload of the revised approved PI to the TGA website	Delay (days)
s22 [redacted]				4
				155
				3
				173
				s22 [redacted]

The rationale for the delays in uploading of the updated PI to the TGA website was requested in writing and not provided. The sponsor commented, s22 [redacted] The inspector noted that two emails, dated s22 [redacted]

s22 respectively, were sent from the TGA Application Entry, Support and Export Section to the s47G(1)(a) for reminders to upload the s22 PI to the TGA.

The sponsor also confirmed that no deviations were opened for these variations to record the non-compliance with a mandatory regulatory timeline.

The delay represented non-compliance with a mandatory timeline imposed by the TGA. There was no evidence to verify that the sponsor had proactively identified this non-compliance and sought to take steps to avoid the reoccurrence and ensure compliance with the legal pharmacovigilance requirements.

Furthermore, despite sponsor inclusion of s22 in the submission s22 the revised PI was still not lodged with the TGA s22

The approval letter for s22 stated:

s22

A search of the publicly facing TGA website on s22 revealed that an outdated version of the sponsor PI for s22 was published and available to the public. This version did not include the TGA approved addition of s22 Therefore, this example represented sponsor non-compliance with the approval letter as well as sponsor provision of out-of-date safety information to the public.

1.3. Delayed uploads of updated CMI to the TGA website following TGA approval

In accordance with the conditions of registration, if the related CMI documents needs to be updated as a consequence of the change to the approved PI, the sponsor **MUST** lodge the updated CMI with the TGA within 2 weeks of the date of the changed PI.

During the inspection, three examples of delayed lodgement of updated CMIs by the sponsor to the TGA website were identified as outlined in the table below.

Product	ARTG Number	Submission number of safety variation to the TGA	Date of the TGA approval of the variation	Date updated CMI was uploaded to the TGA website	Time post approval for upload of CMI to TGA website (days)
s22					156
					69
					34

The sponsor informed that challenges with loading the s22 CMIs to the TGA eBusiness Services were encountered and worked on by both the TGA and s22 However, the TGA Application Entry, Support and Export Section in the TGA did not receive any correspondences from the sponsor regarding issues with s22 No deviations were recorded in the sponsors QMS regarding these examples of regulatory non-compliance.

1.4. Non-maintenance of generic medicine PI with innovator PI (non-marketed products)

In accordance with the Specific conditions of registration for generic products, sponsors **MUST** update PI and CMI documents within one month of safety-related changes made by the innovator.

According to the *Pharmacovigilance Guidelines*, sponsors MUST meet your pharmacovigilance reporting responsibilities for all the medicines you have registered or listed on the ARTG. This is regardless of their Australian marketing status.

The sponsor did not maintain PIs for medicines registered on the ARTG post-approval, until the time that supply commenced, and the medicine was marketed. At the time of the inspection this impacted s22 ARTG entries.

On s22 the following instruction was added to local procedure s47

s47

Prior to s22 , the sponsor did not explicitly outline a process regarding maintenance of PI for non-marketed medicines in any procedure.

The sponsor confirmed that no safety-related variations had been submitted to the TGA for non-marketed products within the last 2 years, in line with the process described in s47 s47 his represented non-compliance with the condition of registration for generic products to update their PI and CMI within ONE month of safety-related changes made by the innovator. The sponsor explained that they believed that their approach was in line with the risk-based regulatory approach of the TGA and that the risk to the patients (of not updating the non-marketed PIs) is low.

Appendix V presents an overview of examples of sponsor PIs for non-marketed products, that were not maintained in line with safety-related updates to the innovator PI.

1.5. Delay in aligning CMI to the updated PI

In accordance with the conditions of registration, there is a continuing obligation to ensure that at all times the CMI complies with the statutory requirements, including consistency with the PI. If the related CMI document needs to be changed as a consequence of the change to the approved PI, the sponsor **MUST** lodge the updated CMI with the TGA **within 2 weeks** of the date of the changed PI. In the case of changes relating to the safety or safe use of the product, more rapid change of the CMI may be warranted.

The s22 CMI available on the TGA website at the time of the inspection, s22 , did not align with the innovator product, s22 CMI also published on the TGA website with date of

preparation s22 Moreover, the s22 CMI did not fully reflect the associated safety related changes to the s22 PI.

The s22 CMI included the following wording:

s22

The inspector noted that the updates in the s22 CMI aligned with the approved PI and the recommendation included in the s22 update s22

The following wording regarding s22 were included in the s22 CMI, date of preparation s22 :

s22

It was noted that the sponsor did update the s22 PI with the safety-related information associated with the same EMA request via TGA s22 submitted with a delay to the TGA on s22 and approved by the TGA s22 However, the corresponding updates to the CMI did not include references s22 nd the update to the s22 CMI did not fully align with the wording provided by the EMA.

The sponsor informed that the product was currently supplied in Australia at the time of the inspection and that between s22 the supply volume for s22 was s22 To ensure the safe use of medicines, it is necessary that CMI available to healthcare professionals and patient are kept up-to-date.

1.6. Deficiencies in processes for the maintenance of PI and fulfillment of TGA requirements towards RSI

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

If you are a sponsor of a generic medicine, it is a condition of registration that you make a submission to the TGA, to align the PI document of your generic product with the Australian innovator PI document, within one month of the date of approval of the safety-related update to the Australian innovator PI document. This is to ensure that safety-related information is consistent in all Australian products containing the same active ingredient, for quality use of medicines by patients and healthcare professionals.

Under paragraph 28(5)(ca) of the Act, you **MUST** retain records pertaining to the reporting requirements and safety for your medicine. Information relating to pharmacovigilance activities and the safety of the medicine include reference safety documents. These **MUST** be retained indefinitely for the life of the medicine and for a period of 10 years after removal from the ARTG for registered medicines. General safety information on your medicine, including documentation regarding changes to reference safety information should also be retained indefinitely for the life of the medicine. We may also ask to review these records on request, or as part of the Pharmacovigilance Inspection Program.

A broad range of deficiencies with the sponsor processes for the maintenance of RSI were identified during the inspection. The written processes and systems implemented during s22 were either incomplete or inaccurate compared to TGA requirements or were not followed. These deficiencies were a likely causative factor for the non-compliance described in this overarching deficiency.

1.6.1. Deficiencies in the process for submission of safety-related variations to the TGA

During the inspection the sponsor s47G(1)(a) informed that until recently, local procedure s47 was the only SOP followed in relation to maintenance of RSI for s22

s47 stated the following in relation to maintenance of generic medicine PIs:

> s47

However, the SOP did not specify how often s47G(1)(a) should monitor the TGA website. Therefore, this process did not facilitate compliance with the timeline for identification and submission of safety-related updates as specified by the TGA which requires a submission to the TGA, to align the PI document of the generic product with the Australian innovator PI document, within one month of the date of approval of the revised innovator PI.

Furthermore, the SOP did not provide any instruction regarding **how** to review the TGA website, track and record reviews and outcomes or how to track the frequency of the activity, therefore the sponsor procedure was considered incomplete and not well-defined. The lack of clarify in the SOP may have contributed to the delays in updating the generic PI, following the innovator PI update, as discussed in Critical Deficiency 1.1. It was unclear how the SOP could ensure that the responsibilities, requirements, and timelines related to the management of RSI would be understood by the relevant staff and be executed consistently to the expected standard for compliance. Consequently, the s47G(1)(a) s47G(1) informed that there was no set frequency for review of the TGA website for revised Innovator PIs and that this task was done as much as possible and not always documented. A methodology for identification of updated innovator PIs on the TGA website and subsequent review and assessment regarding the impact to the sponsor product PI was verbally described in the inspection however these actions were not outlined in any written procedure. In addition, a number of informal tools and instructions had been developed outside of the sponsor QMS including:

- An Excel spreadsheet
- Informal checklist based on experience of the s47G(1)(a)

The s47G(1)(a) informed that since starting in the role s22 had implemented an Excel spreadsheet for "personal use" only to facilitate reviews of the TGA website for innovator PI updates including the innovator brand name, date of last PI revision and free text assessment comments regarding whether a variation was required. It was highlighted that the spreadsheet was not version controlled and not consistently completed. No reference to this spreadsheet nor checklist was included in any sponsor written procedure.

It was noted that procedure s47 specifically quoted the information regarding the timeline for sponsor submission of a variation from the verbatim *TGA Frequently Asked Question* with reference to the TGA publication of this information in January 2021. This SOP was provided to the inspectors as a pre-inspection document response, but the sponsor thereafter clarified that the procedure was not relevant to s22 products in relation to maintenance of RSI until s22 was authored by a previous QPPVA and trained upon by the current QPPVA which provided evidence that the QPPVA was aware of the *TGA Frequently Asked Questions* publication and the TGA expectations of how sponsors apply the condition of registration and maintain the PI for generic products. However, this was not implemented into s47 . A review of training records confirmed that the sponsor s47G(1)(a) did not undergo training on s47 until s22 when the process was adopted for s22 The sponsor informed that the reason for this change was process improvement for RA processes for maintenance of reference safety information moving forward.

1.6.2. Lack of written procedure for sponsors regulatory obligations post-TGA approval of a revised PI

There was no description for the required actions and associated mandatory timeline for once a TGA approval was received in s47 including:

- no procedure regarding the required review of the CMI to ensure ongoing consistency with the approved version of the PI
- no procedure regarding the required upload of the PI and CMI within two weeks of the date of approval of the variation and within 2 weeks of the date of the changed PI respectively.

During the inspection interview, numerous key activities were verbally described as part of the RSI maintenance process followed by the s47G(1)(a) however these were not outlined in s47G These included:

- consultation with the s47G(1)(a) regarding the content e.g. formatting of the CMI
- notification and provision of the revised PI and CMI to the s47G(1)(a)
- upload of revised PI and CMI to the TGA website within mandated timeframes
- spot-check of publicly facing partner websites to verify that the version of the PI had been updated
- record keeping activities relating to sponsor RSI records.

An example was also identified where the sponsor did not follow the documented procedure in s47

Despite this written procedure, on two separate occasions during the interview, the sponsor confirmed that the sponsor did not provide revised PIs to s22 the MI service provider for s22 since s22 accessed the RSI directly from the TGA website.

The sponsor also confirmed that there was no procedure addressing record retention rules at local level for records saved to the s47G(1)(a) on the s47G(1)(a) . This is despite such records being in scope of required and recommended timelines as specified in the *Pharmacovigilance Guidelines*.

1.7. Deficiencies in the procedure for QPPVA oversight for the maintenance of RSI

In accordance with the *Pharmacovigilance Guidelines*, we expect you to have an effective pharmacovigilance system in place in order to update product labels and product information (PI) with new safety information in a timely way.

The QPPVA needs to have adequate understanding of the Australian and global pharmacovigilance processes to allow them to have effective oversight of the entire pharmacovigilance system.

The QPPVA should ensure that the sponsor has an effective pharmacovigilance system in place and complies with the legal pharmacovigilance requirements.

During the inspection, it was identified that written procedure for QPPVA oversight for the management of RSI was incomplete. The sponsor described that QPPVA oversight of the management of RSI was fulfilled by the sponsor s47G(1)(a) sharing results of PI reviews and updates with the QPPVA. Evidence of the s47G(1)(a) being shared with the QPPVA was provided from s22 s22 to substantiate this. The requirement for s47G(1)(a) to maintain this tracker and share it with the QPPVA on a specific schedule and the QPPVAs role with this information was not outlined in any procedure. Without this process clearly described in an SOP, it could not be verified that this process could be conducted in a consistent manner without interruption and delay if the QPPVA or s47G(1)(a) was unexpectedly absent.

1.8. Deficiencies in RSI record keeping

Under subsection 28(5)(ca) of the Therapeutic Goods Act 1989 and Regulation 15A of the Therapeutic Goods Regulations 1990, you **MUST** comply with any record keeping requirements that have been prescribed as a condition of registering or listing your therapeutic good in the ARTG.

In accordance with the *Pharmacovigilance Guidelines*, sponsors **MUST** retain records pertaining to reference safety documents indefinitely for the life of the medicine and for an additional 5 or 10 years after removal from the ARTG for listed and registered medicines respectively.

The TGA Guidance document, *Changing the sponsor of therapeutic goods* sets out the obligations of a new sponsor including record keeping and it is recommended that any person or company proposing to take on responsibility for therapeutic goods in the ARTG ensure that it has access to documents that have been provided to, or by, the TGA about those therapeutic goods.

During the inspection, the current PI for the following s22 products was requested, however the sponsor did not fulfill this request and responded that the current PI was not available:

s22

No rationale was provided for the unavailability of the records. The s22 products were part of a sample of s22 non-marketed products for which the PI was requested and therefore for s22 of the products sampled, the sponsor was unable to comply with their record keeping requirements.

1.9. Inaccuracies in sponsor contact info in RSI

In accordance with the Therapeutic Goods Order (TGO) 91 the name and contact details of the medicine sponsor (or a nominated distributor) **MUST** be included on medicine labels. The name of the sponsor or distributor and sufficient information (...) allow the sponsor or distributor to be uniquely identified so as to facilitate public contact on matters of complaint, use or general enquiry. The contact details must include information such as the city or suburb of the sponsor's/distributor's principal place of business in Australia (...)

Section 6 of the TGO 91 includes a transition period of 12 months in the definition of 'contact details'.

In accordance with the TGA Guidance, *Changing sponsor details in Product Information (PI) and labels of prescription medicines, version 1.0, October 2020*, the sponsor **MUST** apply to change the sponsor details in the PI immediately after a change has occurred.

During the inspection, RSI for seven sponsor products was found to be published on the TGA website and available to the public, which included out-of-date sponsor contact information. Further information regarding these examples is provided in the table below.

Sponsor product (ARTG No.)	Discrepancy in RSI publicly available on the TGA website during the inspection	Date of last revision of the RSI
s22		

s22

The sponsors rationale for the discrepancies in sponsor contact information in the above examples (excluding s22 was,

s22

The rationale did not address the reason for the non-compliance since the referenced TGA Guidance does not specify that non-marketed products are out of scope.

Major Deficiency

1. Deficiencies in Management and Reporting of Significant safety issues

1.1. Failure to identify and notify SSIs to the TGA

In accordance with the *Pharmacovigilance Guidelines*, sponsors **MUST** report all significant safety issues related to their medicine to the TGA within 72 hours. A significant safety issue is a new safety issue or validated signal considered by you in relation to your medicines that requires urgent attention of the TGA.

Other examples of significant safety issues include **safety-related actions by comparable international regulatory agencies** such as:
- the withdrawal or suspension of the medicine's availability
- the addition or modification, for safety reasons, of a contraindication, warning or precaution statement to the product information or label
- the modification or removal, for safety reasons, of an indication

A safety issue leading to international regulatory action is considered to be significant and hence reportable regardless of whether you agree with the recommendations and conclusions of the international regulator.

The sponsor did not report any SSIs to the TGA for s22 products during the inspection sample period. Reviews during the inspection identified s47G(1 examples of comparable oversea regulator (COR) requests for modification of the warning and precaution section of the prescribing information which were not notified to the sponsor by the s47G(1)(a) , did not undergo an SSI assessment by the sponsor and were not reported to the TGA as an SSI. Details of these SSI are detailed in Appendix VI.

This represented a significant number of SSI not reported to the TGA during the sample period as required.

During the inspection interview, it was identified that the sponsor was not receiving all safety issues from the s22 that met or potentially met the SSI definition for subsequent assessment and reporting to the TGA. Due to deficiencies in the CCSI notification process to the sponsor, CCSI updates were not received by the sponsor. The sponsor informed that between s22 there were s22 CCSI updates for all products registered by s22 , of which none were received by the sponsor. Of the s22 CCSI updates, s22 updates were triggered by requests from the s22 and s22 updates were triggered by internal signals analysis. A review of the s22 requests which triggered a CCSI update revealed s22 requests for modification of the warning and precaution section of the prescribing information and these should have been reported to the TGA as an SSI.

The sponsor explained that they had recently discovered that CCSI updates were not being notified to the sponsor from the global signal management team due to an omission of s22 generic products from the s47G(1)(a) . The s47G(1)(a) was used by the s47G(1)(a) to determine which s47G(1)(a) required distribution of CCSI updates based on whether there was an active marketing authorisation in that country. An internal deviation was opened s22 regarding this issue and at the time of the inspection the deviation record was still in open status, and root cause analysis, further assessment as well as remediate actions still needed to be defined.

Sponsors should not rely on CCSI updates to identify SSIs since this is not a timely notification process from the global organisation. The inspector noted that the failures in this process meant that, during the sampling period, there was no reliable mechanism for the sponsor to become aware of or identify SSIs to meet their mandatory reporting obligations to the TGA. As a result, no SSIs were identified and reported to the TGA. Furthermore, deficiencies in global and local procedures relating to the management of SSI (as discussed below) may have also contributed to this deficiency.

1.2. Deficiencies in the process for the management of SSIs

In accordance with the *Pharmacovigilance Guidelines*, the TGA recognise that safety information may be received and processed by your global counterparts before it is disseminated to the local affiliates in Australia for reporting to us. We expect you to have clearly documented internal procedures in place that **ensure expedited communication** of significant safety issues from the global personnel to your relevant Australian personnel for reporting (…) Substantial or inappropriate delays between the global and Australian notification may be considered non-compliance with regulatory reporting timeframes.

If you determine after appropriate assessment that a safety issue is not significant and do not report it, you should document a justification for this decision. We may ask you to provide this documentation at any time. If in doubt about a safety issue, treat it as significant (or contact us for advice).

Under paragraph 28(5)(ca) of the Act, you **MUST** retain records pertaining to the reporting requirements and safety for your medicine. Information relating to pharmacovigilance activities and the safety of the medicine include reference safety documents. These **MUST** be retained indefinitely for the life of the medicine and for a period of 10 years after removal from the ARTG for registered medicines.

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

1.2.1. Deficiencies in the global procedure for the communication of COR safety related actions to the local sponsor

A review of the global process for the communication of s47G(1)(a) safety related requests from global sponsor to the local sponsor revealed that the process did not facilitate timely communication between the global sponsor and the local sponsor. During the inspection, the sponsor explained that safety related actions published by s47G(1)(a) could be communicated from the global sponsor as notification of CCSI updates. s47G(1)(a) safety related requests that resulted in CCSI update were not tracked in the s47G(1)(a) and not managed s47G(1)(a) since additional internal signal evaluation by s22 was generally not necessary.

The timeline for completion of CCSI updates, as set out in s47 , was s22 after the receipt of new safety information. Consequently, global procedures did not facilitate the timely communication of these safety issues to the sponsor for SSI assessment and notification to the TGA as an SSI via a CCSI update pathway.

1.2.2. Deficiencies in the process for SSI assessment and documentation

During the inspection, it was identified that the sponsor's written procedure for the assessment and reporting of SSI was incomplete or not followed. The QPPVA clarified that the sponsor process did not include the documentation of the rationale for the SSI assessment and decision not to report a safety issue as an SSI.

s47

However, s47 did not include any instructions nor any link to another procedure to provide instruction on how to review the weekly website search outcome, and how to document evidence of the review including assessments and retention of records from these reviews. Moreover, the SOP did not specify the timeframe in which to do the review of new sources of SSIs.

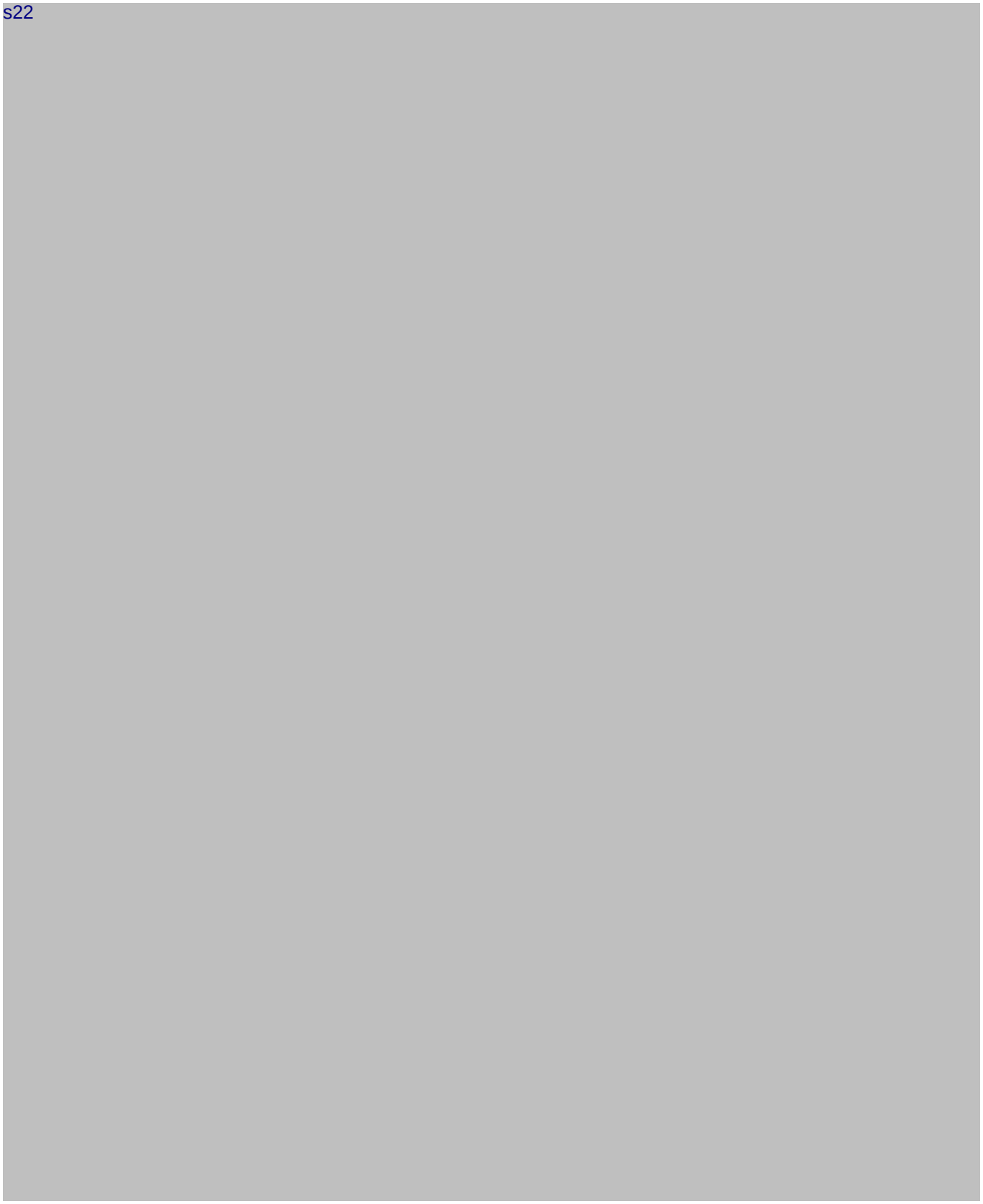
During the inspection interview, the QPPVA verbally described a process of saving email records that s22 had assessed in relation to SSIs, e.g. s47G(1)(a) The QPPVA informed that this needed to be done the same day of receipt . This process was not described in a written procedure..

Evidence revealed that the QPPVA did review the weekly website search result dated s22 which included the SSIs associated with s22 and s22 however the documented SSI assessment stated s22 For the s22 SSI, this could have been attributed to the lack of information within the email communication, however for the s22 SSI, there was a detailed comment within the email which highlighted the request from a COR to update the warning and precaution section of the label,

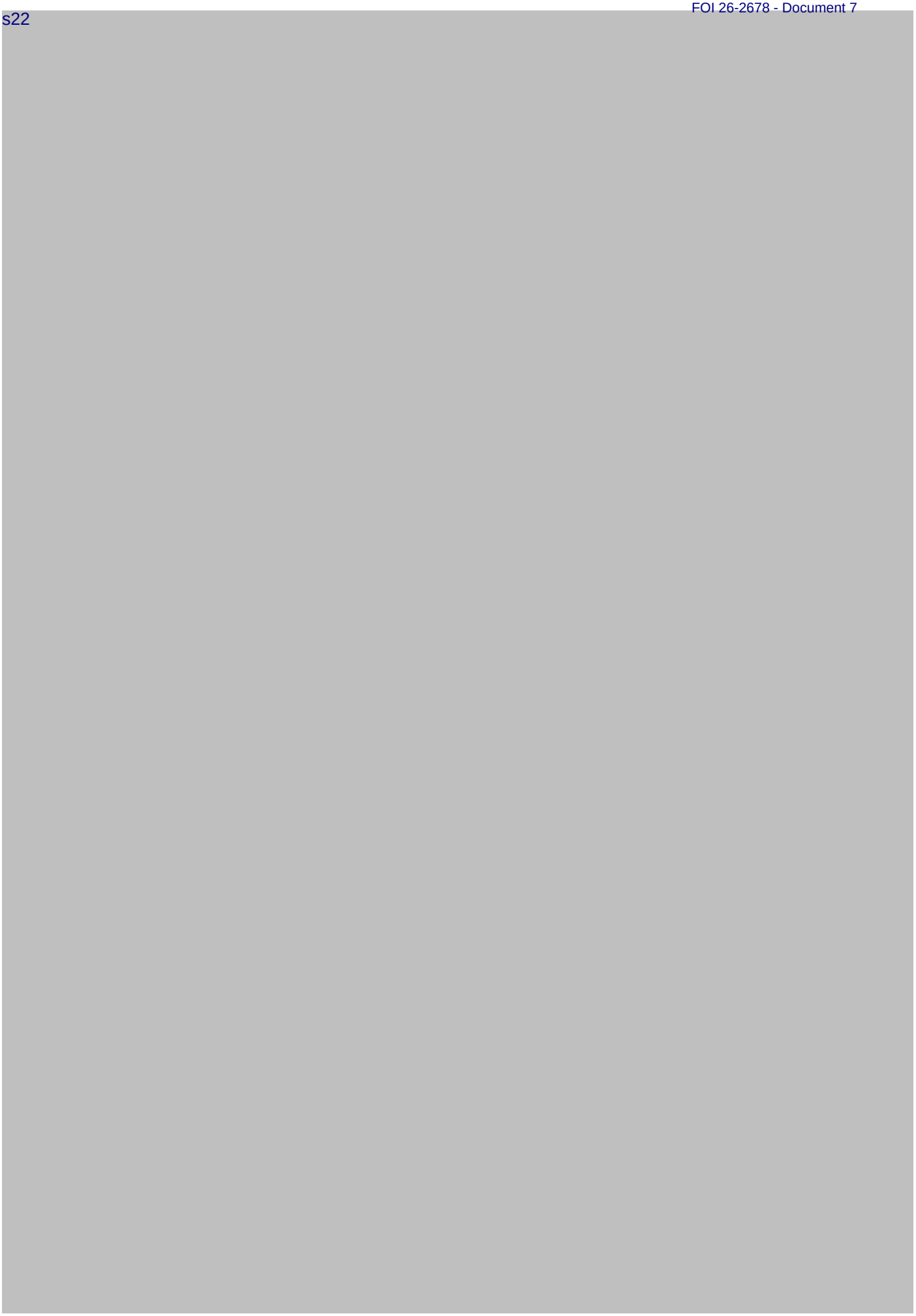
s22

Furthermore, during the interview, the QPPVA referred to a local s22 ” which was implemented from s22 and this tracker was used to document the review and assessment of the weekly website search results. However, how the tracker was applied in the management and reporting of SSI were not described in a written procedure. Without this priority process and implementation of the s47G(1)(a) clearly described in an SOP, it could not be verified that this process could be conducted in a consistent manner without interruption and delay if the QPPVA was unexpectedly absent.

s22



s22



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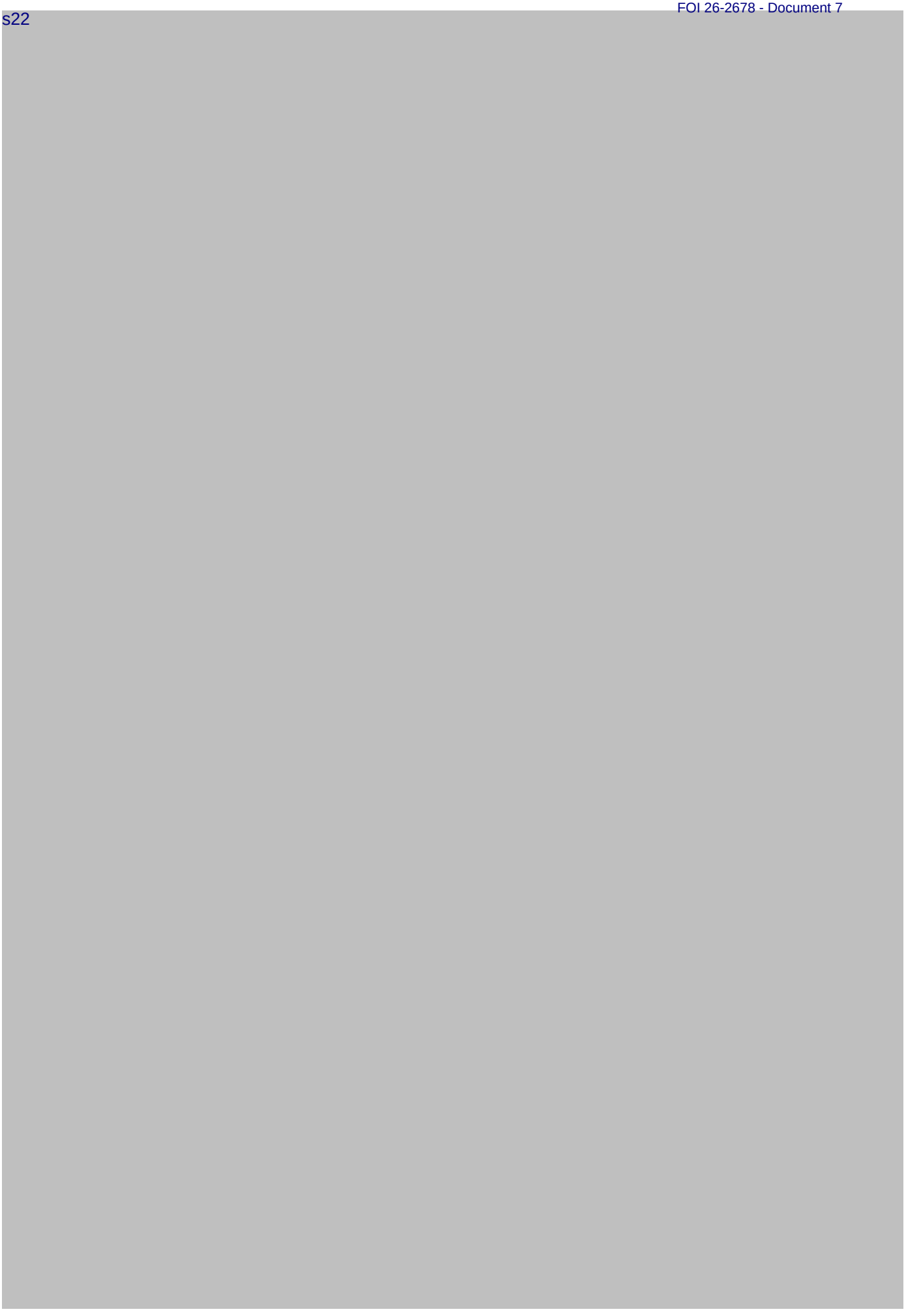


s22

APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Pharmacovigilance Inspection Plan (version 6)

Sponsor name:	s22
Sponsor address:	s22
Inspection type:	Routine systems-based (remote)
Inspection dates:	s22 2023
Inspectors:	s22 (lead inspector), s22 (co-inspector) ancs22 (co-inspector) s22 (observer)

Time (AEST)	Activity	Staff involved
<u>PRE-INSPECTION CALL</u> s22 2023		
2 – 3 pm s22	Pre-inspection meeting Inspection logistics Testing audio, video, screen sharing Q&A	TGA s22 <u>Sponsor Staff</u> s22
<u>DAY 1</u> s22 2023		
9:30 – 10.45 am	Opening meeting Introductions Attendance Scope	TGA s22

Time (AEST)	Activity	Staff involved
s22	Confirmation of Inspection Plan **Company Presentation** Overview of the company and pharmacovigilance system (~30 mins)	Sponsor Staff s22
	Break	
11am – 1pm s22	**Case collection** Spontaneous sources of data Solicited sources of data	TGA s22 Sponsor Staff s22

Time (AEST)	Activity	Staff involved
		s22
1 – 2pm	**Lunch/Break**	
2-3.30pm s22	**Ongoing monitoring** **Management and reporting of significant safety issues to the TGA**	TGA s22 Sponsor Staff s22

Time (AEST)	Activity	Staff involved
3.30-5pm s22	Quality Management System SOPs and other procedures Pharmacovigilance training Record retention and archiving Pharmacovigilance audits Role and responsibilities of the A-PVCP and QPPVA	TGA s22 **Sponsor Staff** s22
DAY 2 s22 2023		
9.30 – 11:30 am s22	**Review of procedures for the management of:** Case entry Case management Follow-up Quality assurance	TGA s22 Sponsor Staff

Time (AEST)	Activity	Staff involved
s22	**Expedited reporting of adverse drug reactions to the TGA**	s22
11.30am-1pm	**Document Review and ad-hoc interview if required**	
1 – 2pm	**Lunch/Break**	
2 pm to 3:30 pm s22	**Maintenance of Reference Safety Information** Overview of the management of variation requests (Sponsor and TGA initiated) Process for the updating PI and CMIs following the identification of new safety information Implementation of PIs and CMIs following approval Package inserts and label	TGA s22 Sponsor Staff s22

Time (AEST)	Activity	Staff involved
		s22
DAY 3 s22 2023		
9am – 5pm	**Document Review and ad-hoc interview if required**	
DAY 4 s22 2023		
10am s22	**Cut-off for document delivery for the closing meeting**	
3.30pm s22	Closing meeting	TGA s22 Sponsor Staff s22

Time (AEST)	Activity	Staff involved
		s22

The times indicated are for guidance only and can be modified to suit

Ad hoc sessions to be included if required throughout the inspection

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
APSS	Australian Pharmacovigilance System Summary
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
CAPA	Corrective and Preventative Action
CCSI	Company Core Safety Information
s22	
COR	Comparable Overseas Regulator
CMI	Consumer Medicine Information
s22	
GSD	Global Safety Database
s22	
MSA	Master Services Agreement
MI	Medical Information
PAC	Post-approval commitments
PI	Product Information
PQC	Product Quality Complaint
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreement
PVIP	Pharmacovigilance Inspection Program
QMS	Quality Management System
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
RA	Regulatory Affairs
RMP	Risk Management Plan
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SRR	Safety Related Request
SSI	Significant Safety Issue
TBS	TGA Business Services
TGA	Therapeutic Goods Administration

APPENDIX IV: Critical Deficiency 1.1

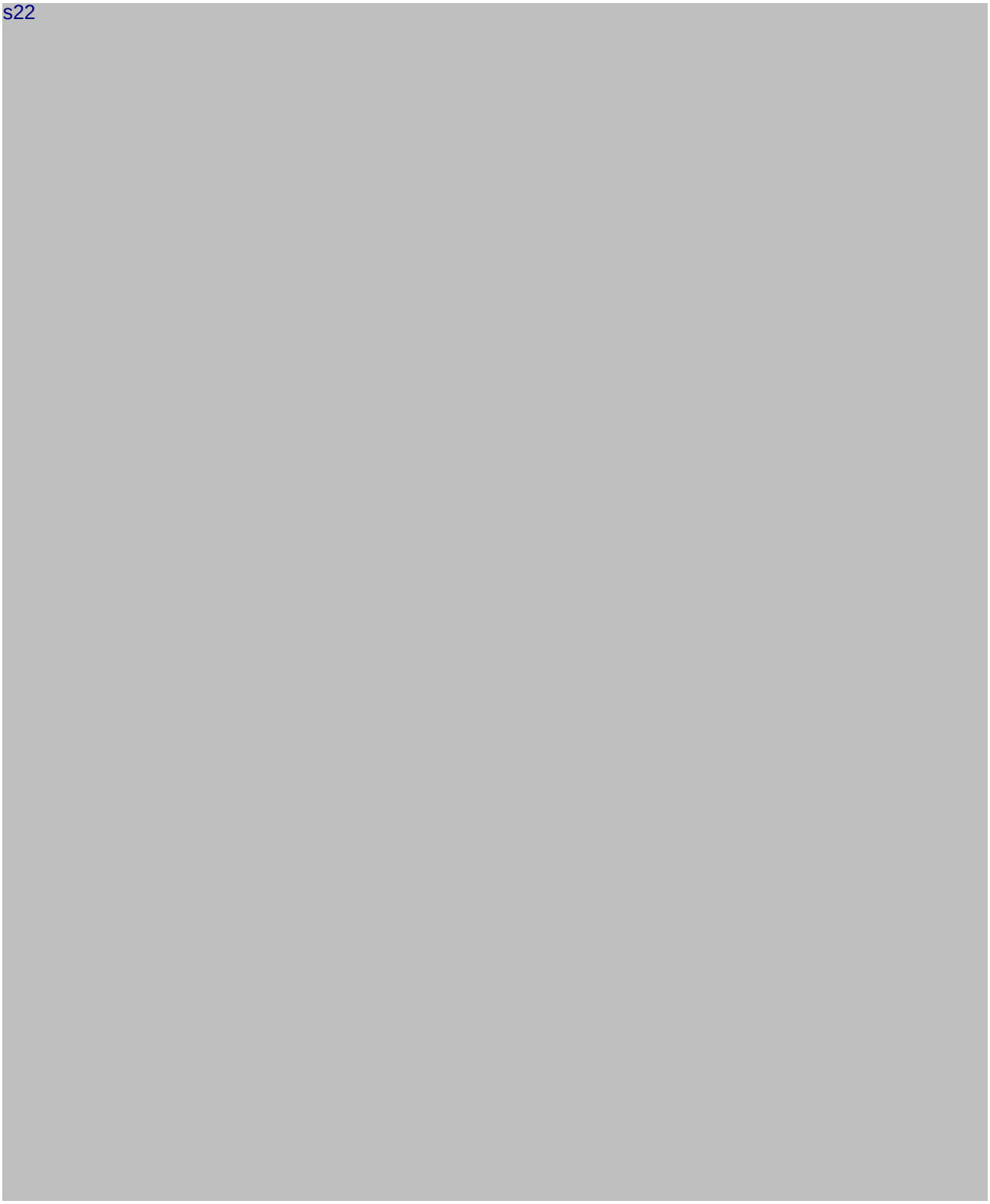
Sponsor product (ARTG No.)	Innovator product / Date of last revision of Innovator PI	Date of sponsor identification of revision of Innovator PI	Summary of safety-related changes added to the sponsor PI (section of the PI)	Date of sponsor submission of safety-related variation (Submission No.)	Delay
s22					8 months 20 days
					3 months 4 days
					2 months, 14 days
					1 month 25 days
					1 month 23 days
					1 month 22 days

s22	
	1 month 2 days
	3 days

APPENDIX V: Critical Deficiency 1.4

Sponsor product (ARTG No.)	Specific condition of registration (approval letter reference) /Submission number	Date of last revision of sponsor PI	Innovator product	Date of last revision on innovator PI	Safety-related updates in innovator PI
s22					

s22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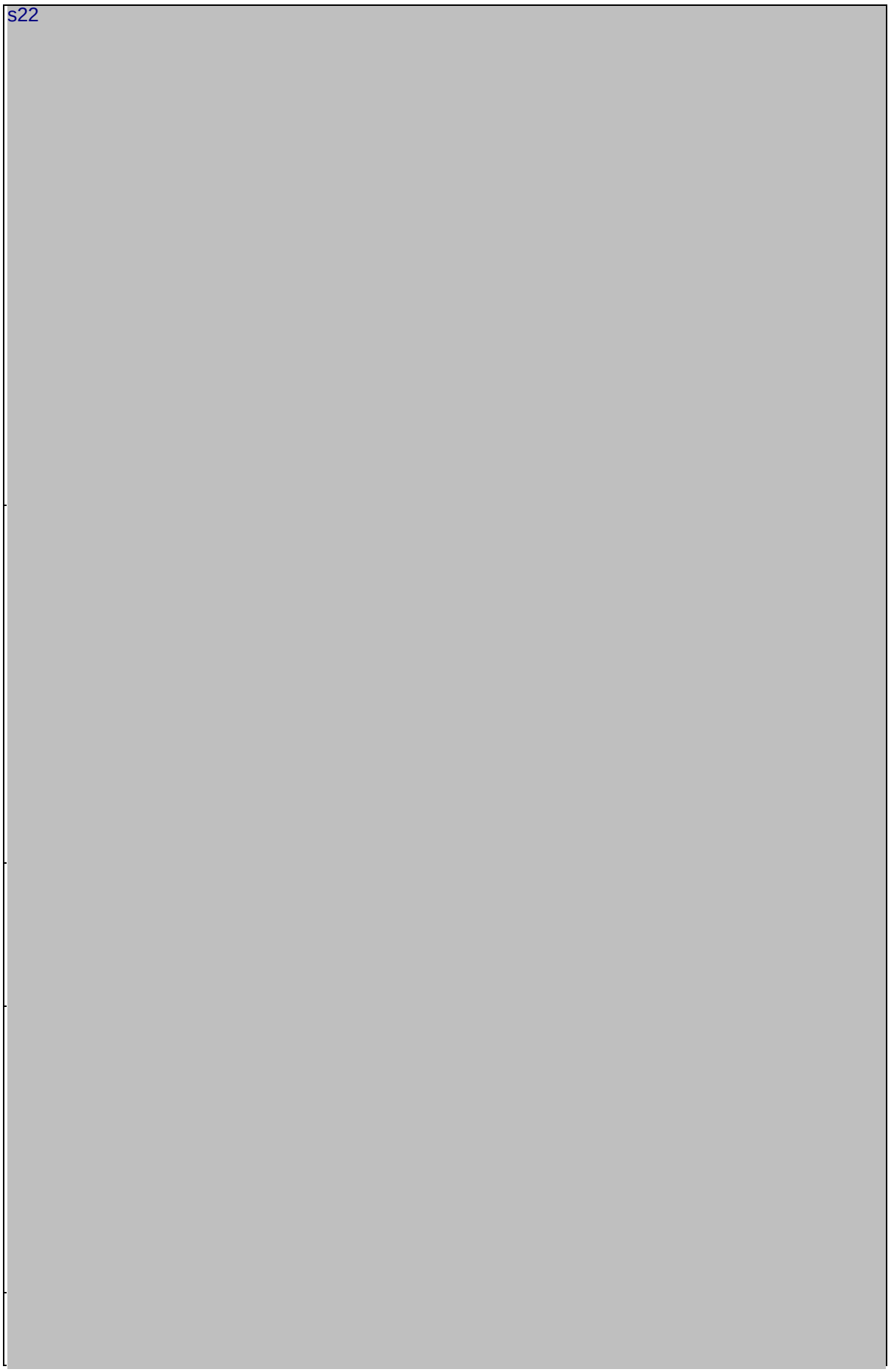
APPENDIX VI: Major Deficiency 1.1

INN	Applicable sponsor product	High level description of safety-related request	Parent company awareness date
s22			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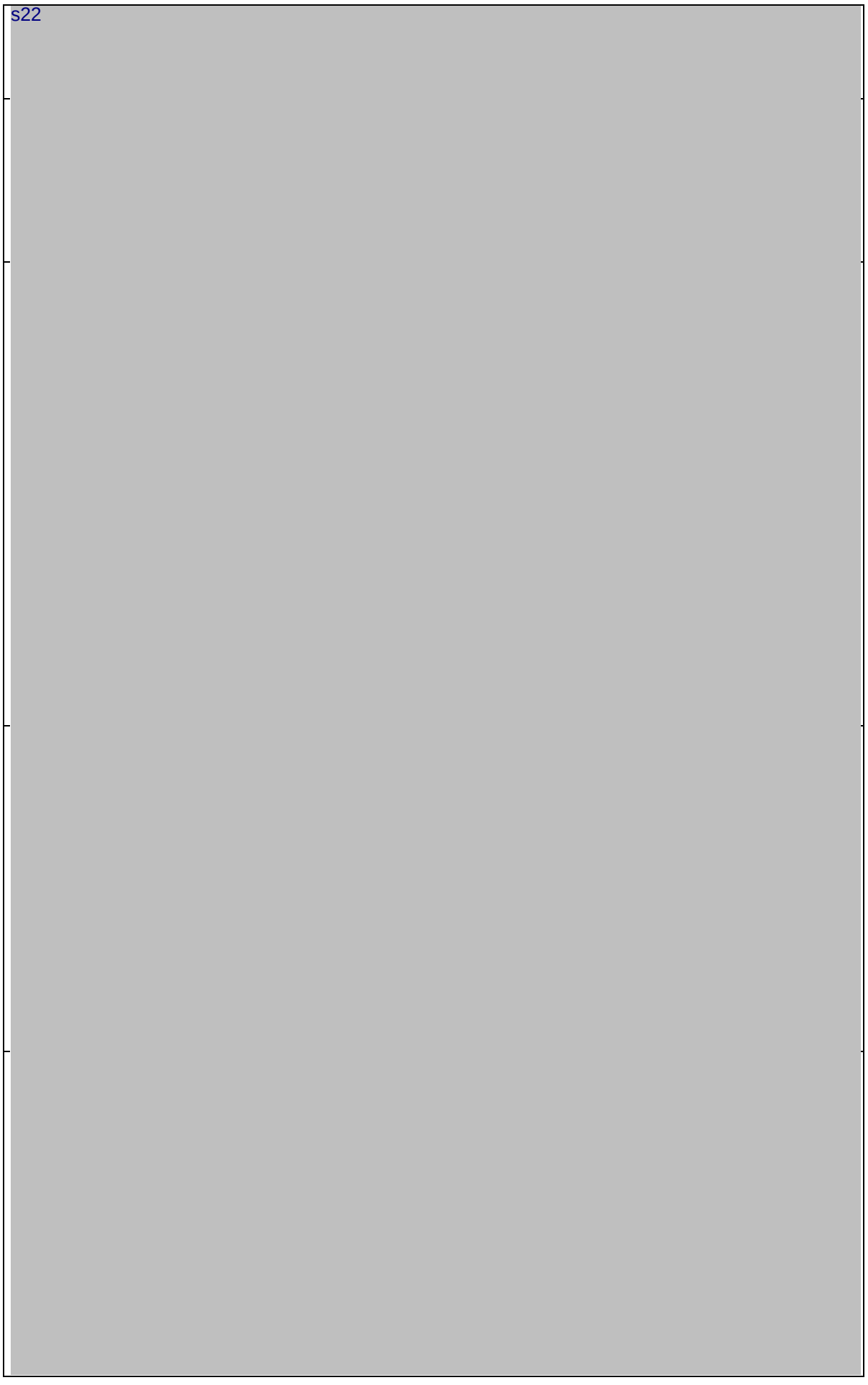
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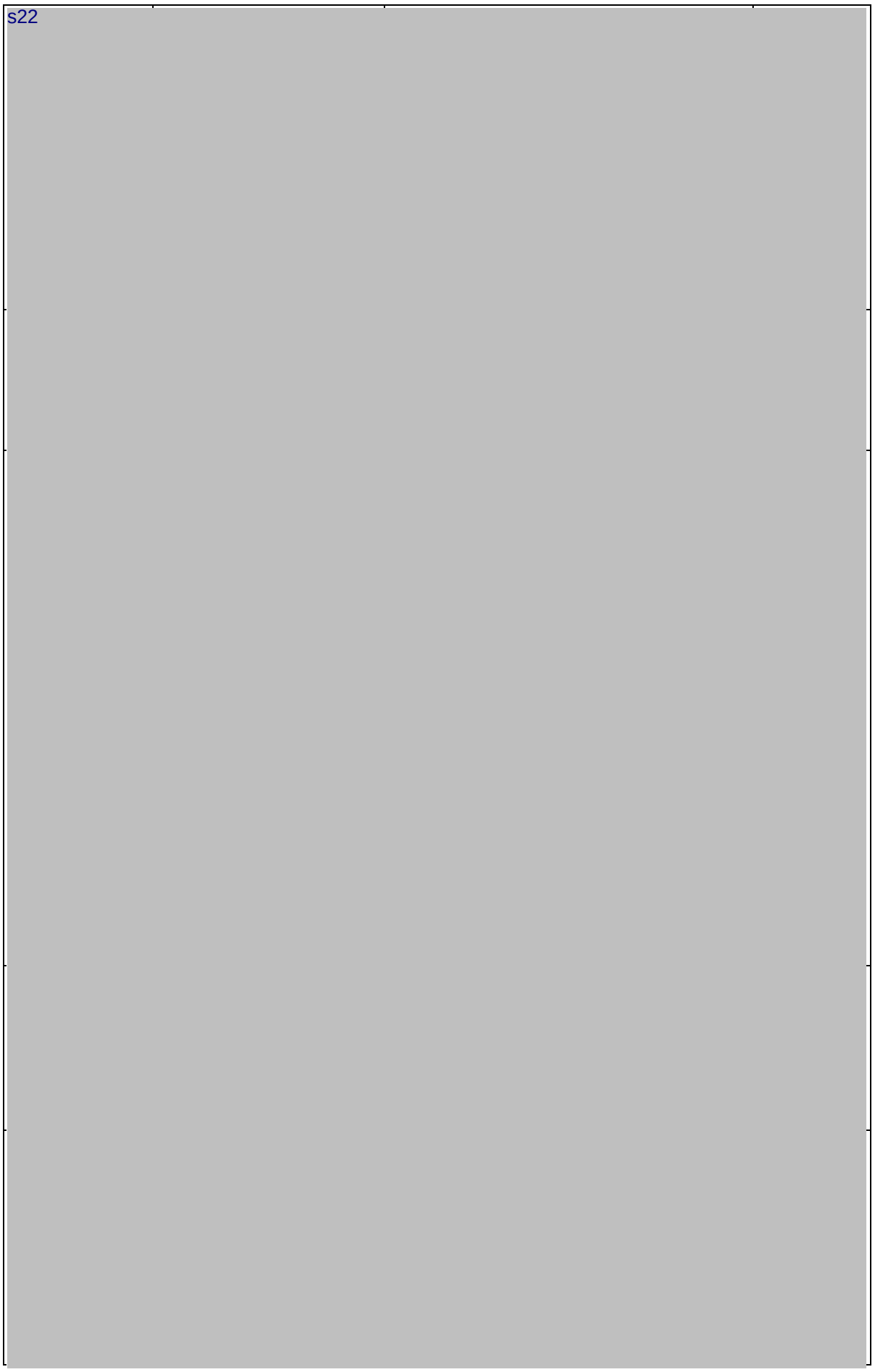
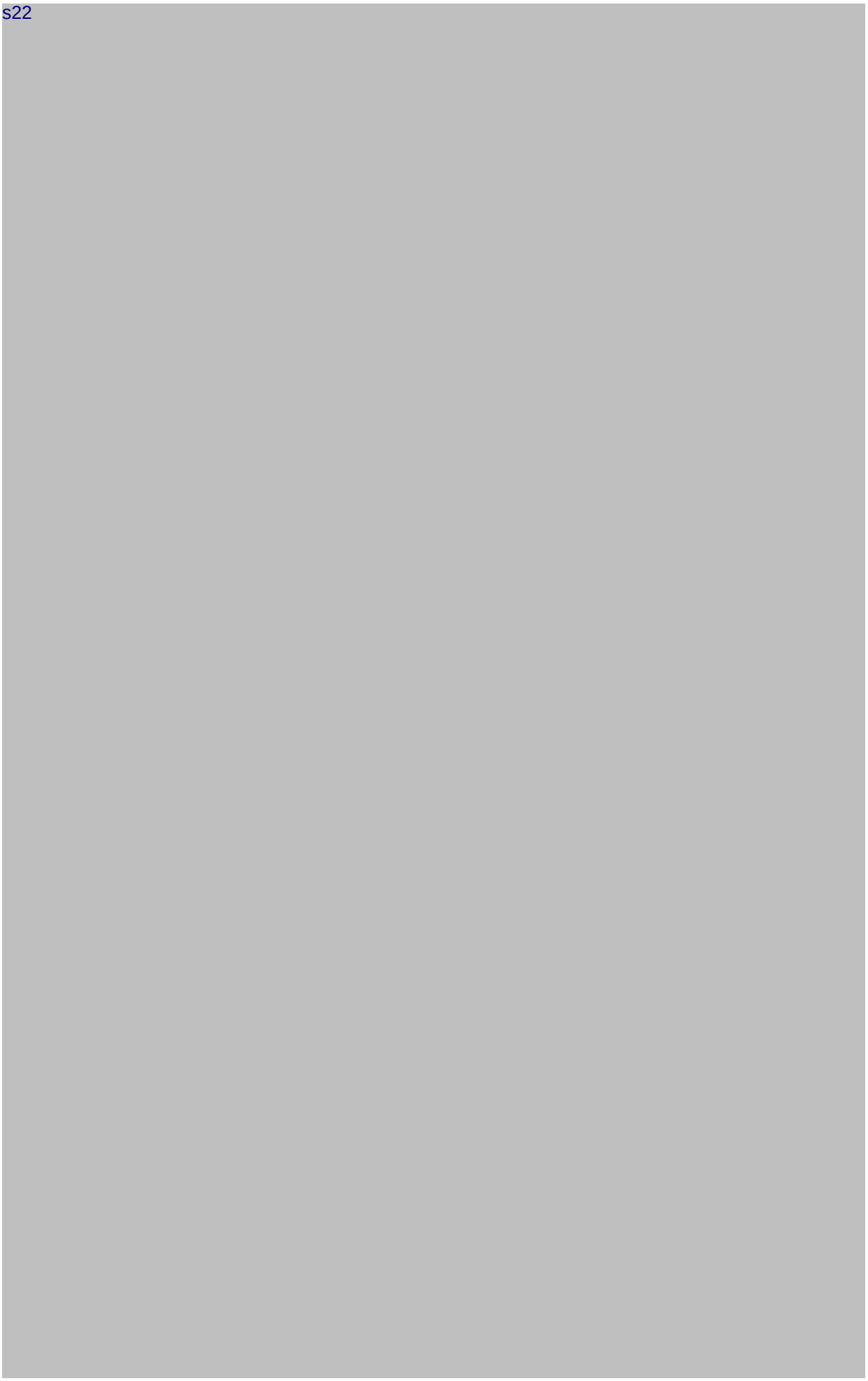

s22

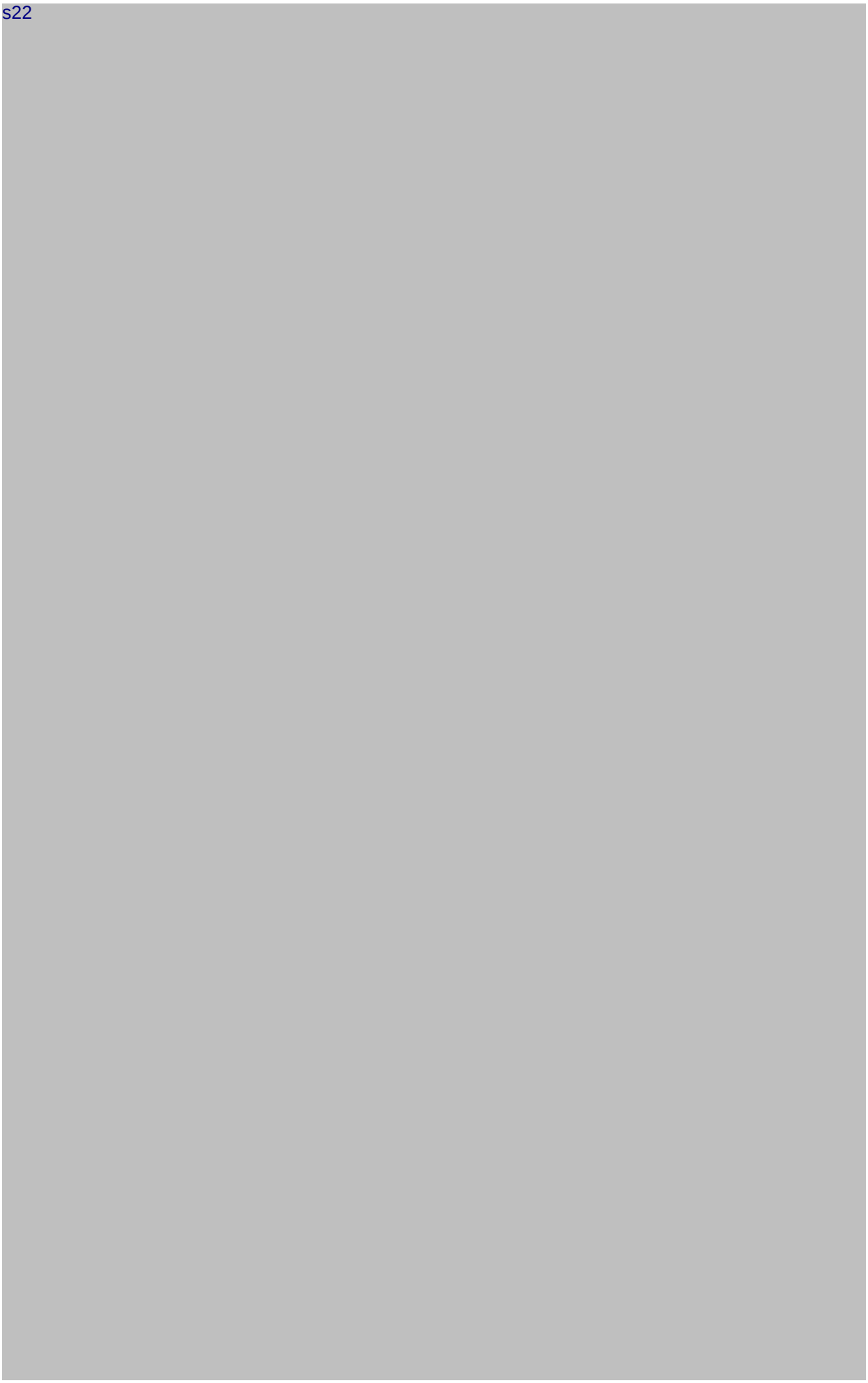
s22

s22



s22

s22


s22


s22

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dear s22

RE: TGA Pharmacovigilance Inspection of s22

Please find attached the inspection report for the hybrid pharmacovigilance inspection of s22 conducted by the Therapeutic Goods Administration (TGA) on s22 s22 2023.

I would like to thank you, and all staff involved, for the courtesy and attention extended during the inspection, which was conducted under the provisions of the *Therapeutic Goods Act 1989*. The purpose of the inspection was to assess compliance with the relevant pharmacovigilance legislation and guidelines and the conditions specified in the relevant approvals for registration or listing on the Australian Register of Therapeutic Goods (ARTG), and any subsequent variations.

It is not possible in an inspection, with a limited time frame, to identify every area requiring attention. It is the responsibility of the sponsor to establish, implement and maintain effective systems and procedures that comply with the:

- *Therapeutic Goods Act 1989* (sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements
- Conditions- standard and specific applying to registered or listed therapeutic goods (section 28 of the *Therapeutic Goods Act 1989*)

Deficiencies should be considered as failures of the quality management system and should be investigated as such. Investigations should focus on the root causes of deficiencies with a view to strengthening the quality assurance system to prevent recurrence.

Deficiencies identified during the inspection are recorded in this report for your attention. References in *italics* are to the relevant legislation and/or guidelines. The definition of each type of deficiency is stated at the conclusion of the report (attached as **Appendix I**).

You are requested to respond to the deficiencies recorded below, within **30 days** from the date of this report, using the attached template of a Corrective and Preventive Action (CAPA) Plan that analyses the root causes of the deficiency, actions taken or proposed to be taken to correct the specific deficiency, and actions taken or proposed to be taken to prevent recurrence. The completion date or target completion date for each action should also be specified in the attached CAPA Commitment Tracker.

For certain deficiencies, you may be requested to submit objective evidence of corrective or preventive actions after their completion dates.

Where objective evidence has been requested for a deficiency but cannot be provided due to the significant time required for completion, a progress report may be requested to ensure that deficiencies are being addressed. In some circumstances, a re-inspection may be required to ensure completion of such activities.

Once all deficiencies have an agreed CAPA in place and the inspection process completed, a letter will be sent to you confirming acceptance of responses and close out of the inspection.

All correspondence regarding the inspection should be addressed to me at Pharmacovigilance.Inspections@health.gov.au.

Yours sincerely

Signed and authorised by
s22

Lead Pharmacovigilance Inspector
Risk Management Section
Pharmacovigilance Branch

s22 2024

Australian Government

Department of Health

Therapeutic Goods Administration

Inspection Report

Sponsor:	s22
Sponsor address:	s22
Main site contact:	s22
Inspection type:	Routine / System-related inspection
Method of inspection:	Hybrid (On-Site and Remote)
Inspection scope:	To assess compliance with the relevant Australian pharmacovigilance legislation and guidelines
Inspection dates:	s22 2023
Inspector/s:	s22 (Lead Inspector) , s22 (Co-inspector), s22 (Co-inspector)
Inspection finding summary:	0 Critical Deficiency 1 Major Deficiency s22
Date report issued to sponsor:	s22
Reference:	E23-324868

Contents

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Introduction

s22 was selected for a routine inspection as part of the TGA's Pharmacovigilance Inspection Programme (PVIP); all acronyms used in this report are listed in **Appendix III**. The purpose of the inspection was to review compliance with currently applicable Australian pharmacovigilance (PV) regulations and guidelines. In particular, reference was made to:

- *Therapeutic Goods Act 1989* (referred to as '*the Act*') sections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (referred to as '*TG Regulations*') Regulation 15A
- Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements (v2.2, January 2021 and v3.0, effective August 2023) (*Pharmacovigilance Guidelines*)
- Conditions – standard and specific applying to registered or listed therapeutic goods (section 28 of *the Act*)

***Company background*:**

s22 (the sponsor), established in s22 and headquartered in s22 is an affiliate of the global s22 organisation based in s22 The s22 organisation s22 established in s22 currently has a presence in over s22 countries and employees s22 . The sponsor employs approximately s22 employees across Australia and have products in the following therapeutic areas: s22 The s22 department in s22 oversees global pharmacovigilance activities and is functionally distributed across s47G(1)(a) PV activities are shared between global s47G(1)(a) and the local s47G(1 s47G(1)(a) team, with some activities outsourced to third party vendors. The s47G(1)(a) team is headed by a global s47G(1)(a) with s47G direct reports.

A summary of the global and local pharmacovigilance activities conducted is presented below:

PV activities performed by s47G(1)(a) team include:

- maintenance of global safety database
- management of s47G(1)(a) and s47G(1)(a)
- signal detection and management
- regulatory surveillance
- quality management system

PV activities performed by s47G(1)(a) team include:

- case collection from spontaneous and solicited reports from consumers, healthcare professionals, local literature, regulatory authorities and legal cases
- PV training
- assessment and submission of significant safety issues (SSI)
- preparation and maintenance of local PV written procedures.
- local vendor management oversight
- follow up safety information requests
- support for local risk minimisation activities.

PV activities outsourced to third party vendors include:

- medical information
- case processing
- global and local literature search/review
- Aggregate safety documents such as risk management plans (RMP) and periodic safety update report (PSUR).

The sponsor had s22 medicine products entered in the ARTG for supply in Australia at the time of the inspection. One of these products, s22 was s22 registered. Within the sponsor's product portfolios, there are s22 products requiring RMPs and s22 with ongoing PSUR submissions to the TGA. s22 products had inclusion in the Black Triangle Scheme applied as a specific condition of registration. s22 patient support program (PSP) and s22 market research programs delivered by third party vendor were ongoing in Australia at the time of inspection.

Brief report of the inspection activities undertaken

Scope of inspection

The inspection was conducted onsite at the company's office in s22 on days 1 and 2 and thereafter, remotely via videoconference. The inspection included a review of both local and global PV systems. Company personnel from s22 and s22 attended the inspection in person and via videoconference.

The inspection was conducted through interviews and review of documents (including searches of PV, medical information and product quality complaint (PQC) databases). The PV topic areas reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as **Appendix II**) and included a review of:

- the collection, processing and reporting of spontaneous and solicited adverse reaction (AR) reports
- ongoing safety evaluation and the management of SSI
- the management of reference safety information (RSI)
- the management of PV post-approval commitments (PAC)
- the role of the Australian Pharmacovigilance Contact Person (A-PVCP) and Qualified Person Responsible for Pharmacovigilance in Australia (QPPVA)
- the quality management system (QMS)

Documents submitted prior to the inspection

The company submitted an 'Australian Pharmacovigilance System Summary' (APSS) document on s22 to assist with inspection planning and preparation. Other specific documents including PV procedures and line listings of Australian adverse event (AE) reports were also requested by the inspection team and provided by the company prior to the inspection.

Conduct of the inspection

In general, the inspection was conducted in accordance with the Inspection Plan (attached as **Appendix II**).

Tabulated Summary of Inspection Deficiencies

Collection, management and reporting of ARs	The procedures for collecting, processing and reporting ARs and special situation reports received from spontaneous and solicited sources, were reviewed during the inspection. This included a review of all Australian reports received by the company between s22 When required, the narrative and source documentation for specific cases were analysed. s22
Ongoing safety evaluation	The procedures for monitoring the ongoing benefit-risk profile of company products were reviewed during the inspection. s22
Management of SSIs	The procedures for managing and reporting SSIs to the TGA were reviewed during the inspection. s22
Management of RSI	The procedures for managing and updating Australian RSI documents, including the Product Information (PI), Consumer Medicines Information (CMI) and product packaging leaflets, were reviewed during the inspection. s22
PAC	The procedures for managing PV PAC, including submission of PSURs, maintenance of RMP documents and implementing RMP commitments, were reviewed during the inspection. Deficiencies related to the management of PAC are described in Major Deficiency 1.
Role of A-PVCP and QPPVA	During the inspection, the roles and responsibilities of the A-PVCP and QPPVA were reviewed. s22
QMS	The QMS, including procedures for implementing PV training and PV audits as well as maintaining PV records and standard operating procedures (SOPs), was reviewed during the inspection. s22

List of deficiencies identified during the inspection

Critical deficiencies

No critical deficiencies were identified during the inspection.

Major deficiencies

1. Deficiencies in PAC

1.1. Failure to comply with PAC

Subsections 28(2B) and 28(3) of the *Therapeutic Goods Act 1989* allow the TGA to impose certain conditions of listing or registration on a therapeutic good when it is entered in the ARTG or at any time while it remains on the ARTG, including when it is suspended.

Under s 21B(2) of the *Therapeutic Goods Act 1989* a person contravenes this subsection if the person does an act or omits to do an act that breaches a condition of the registration or listing of the goods.

The sponsor did not comply with the following specific condition of registration in the s22 approval letter, s22 s22

During the inspection, the sponsor informed that the s22 was available on s22 however it was not submitted to the TGA for evaluation. This constituted a delay of 766 days, s22 . The sponsor explained that the report was not submitted to the TGA due to a s22 ".

The submission of s22 , as requested in the conditions of registration, is important to the ongoing monitoring of the risk-benefit balance of medicines in Australia. Failure to comply with a condition of registration may lead to enforcement actions or removal of medicine from the ARTG.

1.2. Deficiencies in the submissions of updated RMP/ASA to the TGA

In accordance with the TGA *Guidelines on Risk management plans for medicines and biologicals, March 2019*, sponsors **MUST** submit an updated RMP and/or ASA when the TGA request it and whenever there is significant change, such as: **when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.**

You, as the sponsor, are responsible for the RMP, including:
- updating the RMP as new safety information emerges
- communicating this information to the TGA in a timely manner

For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the request of the TGA, then we recommended that the updated RMP/ASA is **submitted within 3 months of the change being accepted by the EMA**.

You should update your risk management plan when new information becomes available regardless of whether your product is marketed.

You should ensure that you always keep your RMP and ASA up to date for your own records and because we may request an updated RMP from you at any time.

1.2.1. Non-submission of updated RMP-ASAs to the TGA (following EMA approval of changes to the summary of safety concerns in the EU-RMPs)

A review of the updated EU-RMP which was pending submission to the TGA revealed one non-submission following EMA approval of significant changes to the EU-RMP. Details of the updated EU-RMP are described in the table below. s22 s22 .

EU-RMP/EMA approval date	EMA approval date	Date of sponsor receipt of EMA approved EU-RMP	Examples of changes to safety concerns approved by the EMA	Sponsor's rationale for not submitting
s22				

The sponsor informed that the missed notification of the updated EU-RMP to the s22 s22 team was reported by s22 staff to the s47G(1)(a) team s22 , during preparation of the inspection, and the deviation was created on s22 The sponsor has also initiated the EU-RMP review and Australia-specific annex (ASA) preparation once they became aware of the existence of the updated EU-RMP.

Subsequently, the updated EU-RMP s47G(1)(a) & ASA s22 was submitted to the TGA on s22 , after the inspection.

1.2.2. Delayed submission of updated RMP/ASAs to the TGA (following EMA approval of significant changes)

During the inspection, a review of all the submissions s22 of updated EU-RMP/ASA from the sponsor to the TGA, following EMA approval in the period s22 , was undertaken. This revealed 16 examples of delayed RMP submission to the TGA. Delays ranged from 21 to 340 days and constituted s22 of the RMP submissions the sponsor made to the TGA. Examples are outlined Appendix IV.

The sponsor's justification for the delays included s22 . However, the RMP guidelines specify that sponsors should update their product's RMP when new information becomes available regardless of whether the product is marketed or not. For seven of the delayed submissions, the sponsor's justification was that the assessment, review and update of the EU-RMP and ASA took in excess of three months. The sponsor confirmed that no deviations or CAPA were created for the delays as s22 However, the sponsor's justification was not consistent with the RMP guidelines, which state that the sponsor is responsible for communicating the updated RMP with new safety information to the TGA in a **timely** manner to ensure safe use of the medicine. A delay of 340 days is not considered timely.

The lack of clear timeframe for the process of assessment, review and update of EU-RMP and ASA may have contributed to this deficiency. Refer to Major Deficiency 1.6 for more details.

1.3. Failure to document the difference in risk management activities between the EU-RMP and ASA

In accordance with the *Risk management plans for medicines and biologicals, Australian requirements and recommendations*, the ASA is required to document any risk management activities not reflected in the EU RMP that are required to adequately address the safety concerns in Australia (such as difference between the EU SmPC and Australian PI in the wording of precautions or contraindications, or additional pharmacovigilance activities required by the TGA).

During the inspection, a review of the s22 revealed that the ASA did not accurately reflect the differences between the statements in the summary of products characteristics (SmPC) and the patient information leaflet (PIL), and Australian PI and CMI, s22 .

The table below, s22 , stated that there were no material differences in routine risk minimisation measures in the EU and Australia to address the safety concern of s22

Safety Concern	Routine Risk Minimisation Activities included in ASA s22	Differences Between EU and Australian Activities with Justification
s22		

However, the routine risk minimisation measures in the s22 also included s22 The sponsor did not outline these differences in the routine risk minimisation activities nor provide a justification for these differences in the s22

1.4. Delayed communication of EMA approved EU-RMP to the sponsor from global headquarters

In accordance with *Risk management plans for medicines and biologicals, Australian requirements and recommendations*, sponsors **MUST** submit an updated RMP and/or ASA when we request it and whenever there is significant change, such as: **when the summary of safety concerns changes, including when the EMA has approved removal or reclassification of safety concerns.**

For changes that have been accepted by the EMA and do not affect additional risk minimisation activities or additional pharmacovigilance activities being undertaken in Australia at the request of the TGA, then we recommended that the updated RMP/ASA is **submitted within 3 months of the change being accepted by the EMA**.

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and **timelines** are well-defined and understood by all personnel involved.

During the inspection, three examples were identified where the notification of EMA approval of the updated EU-RMP was not communicated to the s47G(1)(a) in a timely manner. . The time from EMA approval to notification of s22 ranged from 106 to 158 days. This was considered excessive and did not facilitate the sponsor's compliance with the TGA recommendation of submission to the TGA of significant changes to the EU-RMP within three months of EMA approval. Details of the examples are outlined in the table below.

EU-RMP version/date	Date of EMA approval	Date of Receipt by s22	From EU approval to receipt by Australia (days)	Was the Summary of Safety Concern updated ?
s22			106	Yes
			158	Yes
			157	Yes

Deficiencies in the process for the communication of EMA approval of updated EU-RMP to the s47G(1)(a) team, such as lack of specified timelines, may have contributed to this deficiency. (Refer to Major Deficiency 1.6. for more details)

1.5. Failure to maintain currency of the RMP-ASA

In accordance with the TGA Guidance on *Risk management plans for medicines and biologicals*, throughout the lifecycle of the product, RMPs must be maintained, and important updates submitted to the TGA for evaluation.

You should ensure that you always keep your RMP and ASA up to date for your own records and because we may request an updated RMP from you at any time.

During the inspection, a sample of current additional risk minimisation materials was reviewed against the associated current ASAs. The review revealed that the current s22 has not been updated to reflect the most current version of s47G(1)(a) This activity was a sponsor commitment described in the ASA and a copy of the s47G(1)(a) were included as an appendix to the ASA.

The table below outlines the key differences between the s47G(1)(a) in the ASA and the current s47G(1)(a)

s22

During the inspection, the sponsor confirmed that the ASA may not be updated internally if the additional risk minimisation material had an administrative update.

Both versions s47 stated that the s47G(1)(a) was responsible for the update of

the ASA and required risk minimisation material in collaboration with s47G(1)(a) following EU-RMP update. However, it did not outline the process for updating the ASA or risk minimisation material not triggered by EU-RMP update.

The sponsor is expected to always keep RMP and ASA up to date for their own records.

1.6. Deficiencies in the written procedure for RMP commitments

In accordance with the *Pharmacovigilance Guidelines*, sponsors should develop clear written standard operating procedures (SOPs) for pharmacovigilance to ensure all roles, responsibilities, requirements and timelines are well-defined and understood by all personnel involved.

1.6.1. Deficiencies in the procedure for the communication of EMA approval of EU-RMPs to local safety team

During the inspection, it was identified that the sponsor's written procedure for the notification of EMA approval of EU-RMPs to s47G(1)(a) team did not facilitate sponsor compliance with the TGA's updated RMP submission timelines.

The s47 , which was effective prior to the implementation of s47G(1)(a) , did not stipulate any timeframes for activities such as:

- the notification from s47G(1)(a) to the s47G(1)(a) , after they received notification of approval from s47G(1)(a) , outlined in s47G(1)(a)
- the update to the s47G(1)(a) by the s47G(1)(a) after they received notification from the s47G(1)(a) described in s47G(1)(a) . The update of the s47G(1)(a) triggers an automatic notification to the s47G(1)(a)

The inspector noted that s47 described the responsibility of the s47G(1)(a) of notifying s47G(1)(a) when any new version of EU-RMP received EMA approval. However, it did not stipulate any timeframe for the notification.

Moreover, s47 did not describe the process of how EMA approval of EU-RMPs would be communicated to s47G(1)(a) team in the scenario when s22 was not the market authorisation holder (MAH) in Europe and was not responsible for the authoring of the EU-RMP. The sponsor informed that, in those circumstances, the s47G(1)(a) would communicate with the relevant s47G(1)(a) team member, such as s47G(1)(a) or the relevant s47G(1)(a) of the EMA approval. It was then the s47G(1)(a) responsibility to notify the s47G(1)(a) team, usually via email. However, there was no formal procedure or specific timeframes that described the notification of the EMA approval from the s47G(1)(a) to the s47G(1)(a) team.

The sponsor explained that, for products where s22 was the MAH in Europe, the process for notification of EMA acceptance of EU RMP to local affiliate changed after the implementation of the s47G(1)(a) on s22 . The s47 specified that s47G(1)(a) would review and complete the s47G(1)(a) within 5 days, which triggered the notification of the EMA approval of the updated EU-RMP to the s47G(1)(a) within the s47G(1)(a) intends to expand the same process to products where the parent company is not the MAH in Europe.

The lack of clearly documented processes, including specified timelines, may have contributed to the delays in the communication of EMA approval of EU-RMPs, to the local safety team, as discussed in Major Deficiency 1.4.

1.6.2. Deficiencies in the procedure for the management of updated RMP by local safety team

During the inspection, it was identified that the sponsor's local written procedure for the management of updated RMP submissions were either incomplete or outdated.

Specifically, regarding s47 :

- s47 described the process of the assessment, review and update of the EU RMP and ASA to the TGA. However, it did not stipulate a timeline from receipt of EU RMP update notification to submission of the updated EU RMP and ASA to the TGA.
- s47 stated s47 however the SOP did not stipulate what the timelines should be to ensure compliance with TGA recommendations.
- s47 stated that s47 The sponsor has implemented the use of s47G(1)(a) for the tracking of RMPs from s22 and no longer receive RMP grid notifications.

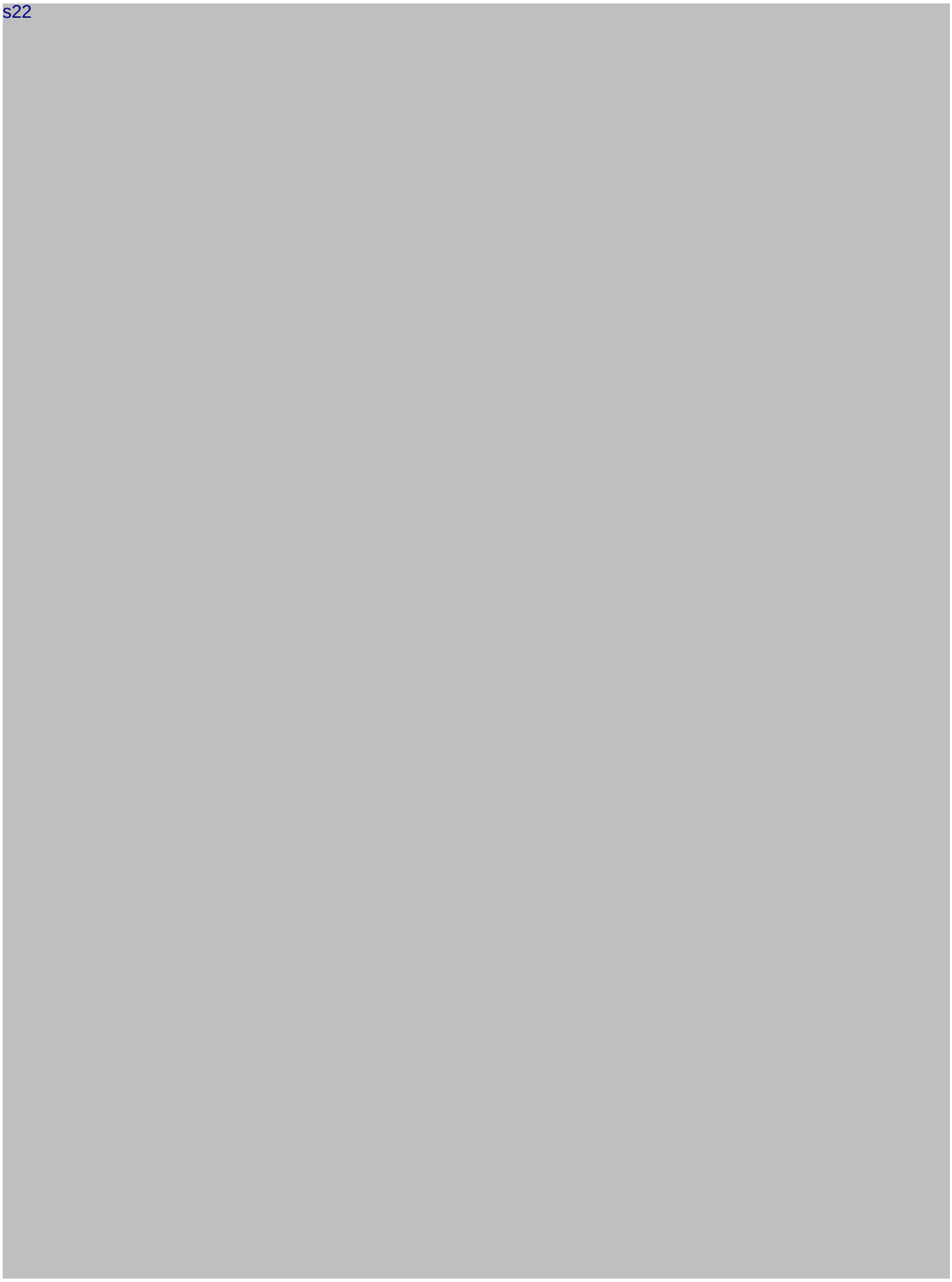
Moreover, s47 did not specify where the assessment of the updated EU-RMP should be documented. During the inspection, the sponsor informed that the s47G(1)(a) record the RMP assessment into the s47G(1)(a). However, the SOP did not reference the s47G(1)(a).

The sponsor informed that the s47G(1)(a) team and s47G(1)(a) team would discuss the submission strategy for the submissions of RMP updates to the TGA. This included consideration of any potential regulatory submissions or ongoing regulatory evaluations which may require an RMP submission, product availability and product launch timelines. These discussions occurred during informal meetings between the two teams. This process was not described in the SOP.

Furthermore, s47, did not specify the timeline from receipt of request to update local RMP or notification of approved EU-RMP to finalisation of local RMP.

The lack of clearly documented processes, including specified timelines, may have contributed to the delays in the submissions of the updated RMPs to the TGA (see Major Deficiency 1.2).

s22



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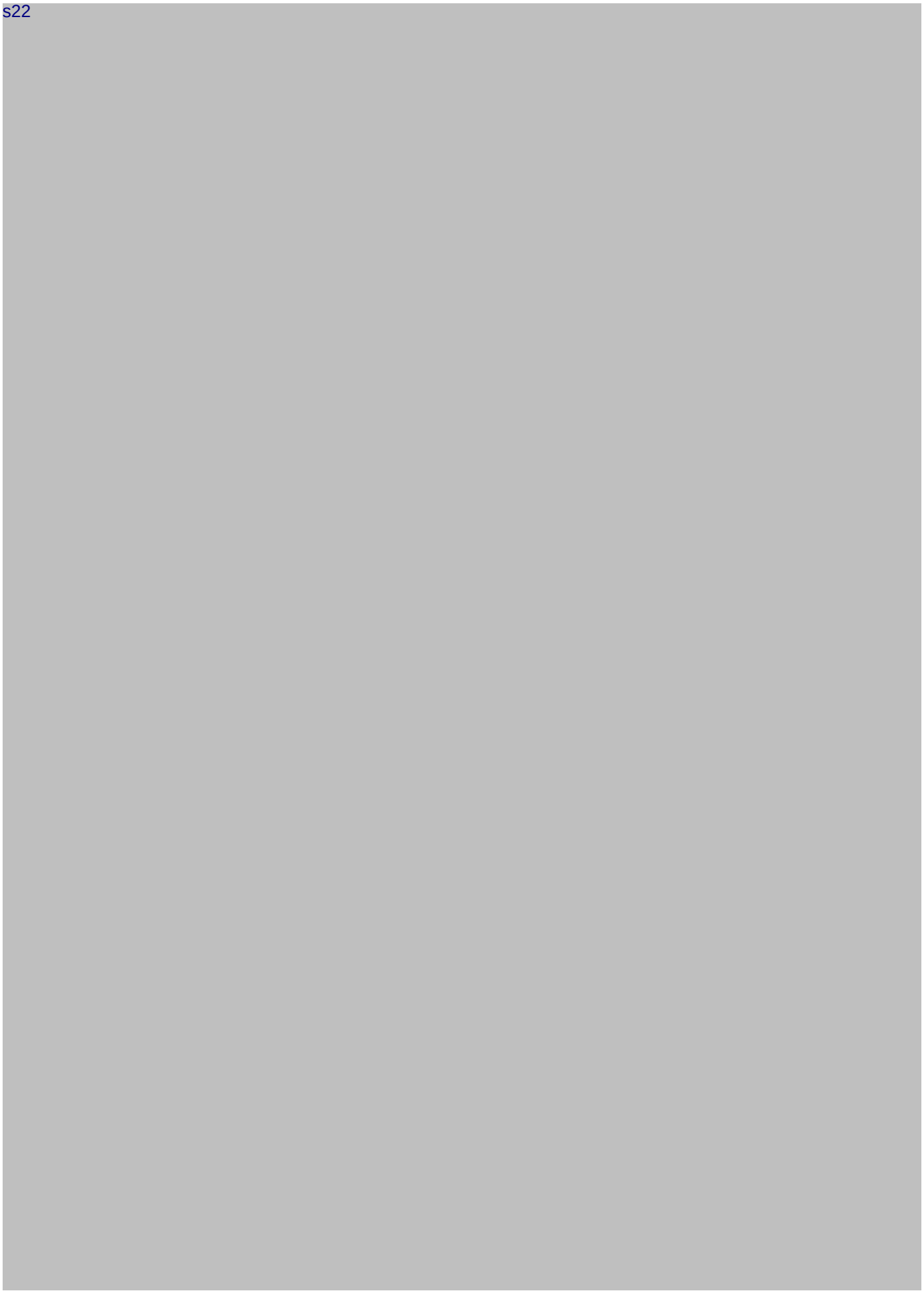

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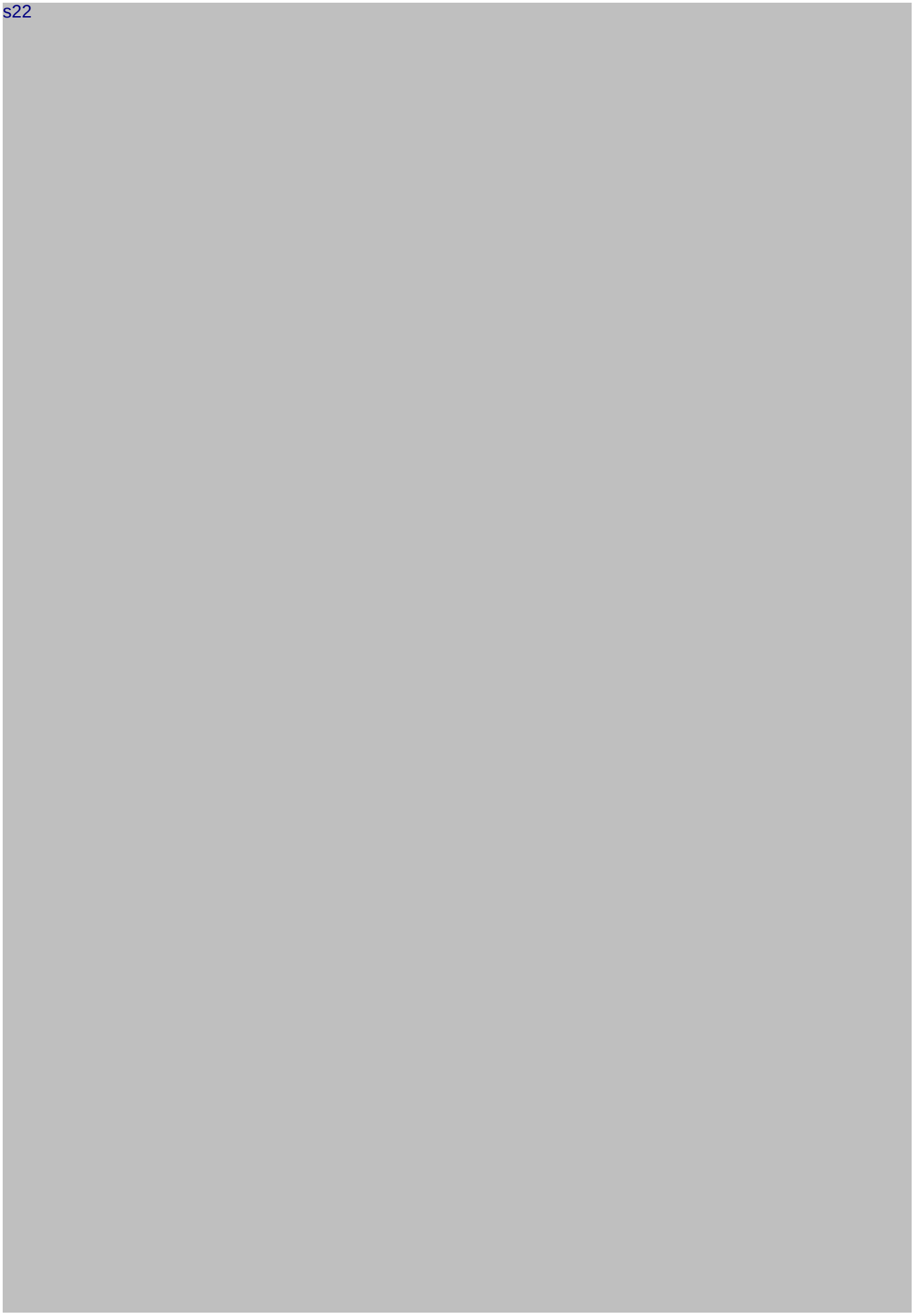
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APPENDIX I: DEFICIENCY GRADING DEFINITIONS

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Comment:

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the medicine. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.

APPENDIX II: PHARMACOVIGILANCE INSPECTION PLAN

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance Branch

Pharmacovigilance Inspection Plan – Version 7

	s22
Sponsor address:	s22
Inspection type:	Routine systems-based (hybrid)
Inspection dates:	s22 2023
Inspectors:	s22 (lead-inspector), s22 (co-inspector), s22 (co-inspector)

PRE-INSPECTION CALL
s22 2023

Time (AEDT)	Activity	Staff involved
10 – 11am	Pre-inspection meeting Inspection logistics Testing audio, video, screen sharing Q&A	TGA s22 Sponsor Staff s22

Time (AEDT)	Activity	Staff involved

DAY 1 (onsite at sponsor address)
s22 2023

Time (AEDT)	Activity	Staff involved
10 – 11am	Pre-inspection meeting Inspection logistics Testing audio, video, screen sharing Q&A	TGA s22
	Company Presentation Overview of the company and pharmacovigilance system (~30 mins)	Sponsor Staff s22
	Tour of office	
	Break	
11:15am – 1:15 pm	**Case collection** Spontaneous sources of data Solicited sources of data	TGA s22 Sponsor Staff s22

Time (AEDT)	Activity	Staff involved
1:15pm – 2pm	**Lunch/Break**	
2 – 4pm	**Maintenance of Reference Safety Information** Overview of the management of variation requests (Sponsor and TGA initiated) Process for the updating PI and CMIs following the identification of new safety information Implementation of PIs and CMIs following approval Package inserts and label	TGA s22 Sponsor Staff s22
4-5pm	**Document reviews and ad-hoc interviews if required**	
	DAY 2 (onsite at sponsor address) s22 2023	
9:30 to 10:15	**Patient Support Program**	TGA s22 Sponsor Staff s22
10:15 – 12:00pm	**Post-approval pharmacovigilance commitments** Conditions of registration RMPs/ASAs PSURs	TGA s22 Sponsor Staff s22

Time (AEDT)	Activity	Staff involved
		s22
12:00 to 12:30	**Lunch/Break**	
12.30 – 1:45 pm	**Ongoing monitoring** **Management and reporting of significant safety issues to the TGA**	TGA s22 Sponsor Staff s22
1.45 to 2:00	**Break**	
2: 00-4:15 pm	**Review of procedures for the management of:** Case entry Case management Follow-up Quality assurance **Expedited reporting of adverse drug reactions to the TGA**	TGA s22 Sponsor Staff s22

DAY 3 (remote)

s22 2023

Time (AEDT)	Activity	Staff involved
11-11:30pm	**Interview with s22 MSL and commercial team**	TGA s22 Sponsor Staff s22
11:30am to 5pm	**Document reviews and ad-hoc interviews if required**	
	DAY 4 (remote) s22 2023	
12pm to 1:00 pm	**Interview with s22**	TGA s22 Sponsor Staff s22

Time (AEDT)	Activity	Staff involved
		s22
1:00 - 2pm	**Document reviews and ad-hoc interviews if required**	
2:00 to 3:00	**Role of QPPVA and APVCP**	TGA s22 Sponsor Staff s22
3:00 to 5:00	**Document reviews and ad-hoc interviews if required**	
	DAY 5 (remote) s22 2023	
8:30 am to 9:00 am	Global RMP updates process	TGA s22 Sponsor Staff s22
9:00 am to 4.00 pm	Document reviews and ad-hoc interviews if required	
4.00pm	Closing meeting	TGA s22

Time (AEDT)	Activity	Staff involved
		Sponsor Staff s22

The times indicated are for guidance only and can be modified to suit

Ad hoc sessions to be included if required throughout the inspection.

APPENDIX III: LIST OF ACRONYMS

The following acronyms were used in this report:

AE	Adverse Event
APSS	Australian Pharmacovigilance System Summary
A-PVCP	Australian Pharmacovigilance Contact Person
AR	Adverse Reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-Specific Annex
s47G(1)(a)	
CAPA	Corrective and Preventative Action
CDS	Company Datasheet
CMI	Consumer Medicines Information
EMA	European Medicines Agency
s47G(1)(a)	
EU	European Union
s47G(1)(a)	
MAH	Market Authorisation Holder
s47G(1)(a)	
PAC	Post-Approval Commitments
PI	Product Information
PIL	Patient Information Leaflet
PQC	Product Quality Complaint
PSP	Patient Support Program
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVIP	Pharmacovigilance Inspection Program
QMS	Quality Management System
QPPV	Qualified Person Responsible for Pharmacovigilance
QPPVA	Qualified Person Responsible for Pharmacovigilance in Australia
RCA	Root Cause Analysis
RMP	Risk Management Plan
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SMPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
TGA	Therapeutic Goods Administration

APPENDIX IV: MAJOR DEFICIENCY 1.2

EU-RMP version	Date of EMA approval	Date of sponsor receipt of EMA approved EU-RMP	Was the Summary of Safety Concern updated ?	TGA submission date	Delays	Sponsor's rationale
s22					98	Update to the TGA scheduled to occur prior to product launch
					100	Delayed notification of updated EU-RMP from local to global
					115	s47G(1) reporting responsibilities transferred from s22 s22 and submission was completed ASAP
					162	Pending s47G(1)(a) submission, received confirmation that s47G(1)(a)
					65	The assessment, review and update of the updated EU-RMP took in excess of three months
					36	The assessment, review and update of the updated EU-RMP took in excess of three months
					259	Decision made to submit updated RMP with PSUR submission
					104	Timing was discussed and determined with s47G(1)(a) but no rationale for the delayed was provided.
					126	The assessment, review and update of the updated EU-RMP took in excess of three months
					21	The assessment, review and update of the updated EU-

s22		
		RMP took in excess of three months
	51	The assessment, review and update of the updated EU-RMP took in excess of three months
	267	The assessment, review and update of the updated EU-RMP took in excess of three months
	107	Decision was made to submit updated RMP with the next PSUR submission
	202	The assessment, review and update of the updated EU-RMP took in excess of three months
	166	Decision was made to submit the updated RMP following completion of s47G(1)(a)
	340	Decision made to submit updated ASA only when the s47G(1)(a)

s22