Australian Government
Department of Health
Therapeutic Goods Administration

Good Manufacturing Practice annual report 2019-20

Version 1.0, November 2020

TGA Health Safety Regulation

Contents

What we do

The Therapeutic Goods Administration (TGA) safeguards and enhances the health of the Australian community through effective and timely regulation of therapeutic goods. The Manufacturing Quality Branch (MQB) works to ensure manufacturers of medicines, as well as blood and blood components, human tissue and cellular therapy products, meet appropriate Good Manufacturing Practice (GMP) quality standards.

This involves both the physical inspection of manufacturing facilities in Australia and overseas as well as the desktop assessment of facilities where suitable inspections have been carried out by comparable overseas regulators and where necessary, initiation of appropriate regulatory action to ensure compliance with the quality standards.

A critical component of this work is also the management of recall actions for therapeutic goods in Australia. A separate annual report has been produced covering these aspects of the MQB work program.

Highlights

- The Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to GMP for medicinal products Version 13 was fully implemented on 1 January 2020 after the one year transitional plan and updates to all the required technical guidance documents.
- On Thursday, 21 November 2019, MQB hosted the TGA's second Industry Forum on GMP. This is the largest face to face event currently hosted by us, with 465 delegates in attendance on this occasion. The program included presentations by TGA experts on GMP clearance, common inspection deficiencies, data integrity in the laboratory and how the work of the TGA's laboratories intersect with GMP requirements.
- To ensure the ongoing supply of quality medicines, blood and human tissue products from Australian and overseas manufacturers in response to the COVID-19 pandemic, TGA undertook a broad range of activities to assist with ensuring their continued operation. This included the development of processes to enable inspectors to undertake remote and/or hybrid GMP inspections where suitable, in place of on-site inspections.

Ensuring manufacturing quality

The information in this report provides insights into manufacturing quality regulatory activity, which contributes to Outcome 5: Regulation, Safety and Protection in the Health Portfolio Budget Statements 2019-20, and TGA business plan 2019-20 objective regarding the ongoing monitoring of the safety, efficacy performance and quality of medicines, medical devices biologicals and other therapeutic goods.

GMP licensing and certification

Enquiries

Assistance to applicants

Australian sponsors have access to specialist advice in relation to their GMP applications for Australian manufacturing licences and GMP Certificates (overseas manufacturers) through the GMP@health.gov.au email address and TGA contact phone lines.

MQB manages approximately 950 enquiries a year through the GMP enquiry mailbox.

In 2019–20, 70% of the enquiries received were general enquiries related to the regulatory requirements of the GMP application process, 21% were technical GMP related enquiries that are referred to specialist inspectors for review and the remaining 9% required technical review of the licensing requirements.

In the early stages of the COVID-19 pandemic, we received a large volume of emails and phone calls in relation to the regulation of, and requirements for hand sanitisers. In MQB, there were a total of 358 emails responded to for the period from March to May 2020. Updates to the TGA website on the GMP requirements for manufacturers of hand sanitisers have seen the number of enquiries fall to just 35 emails in June 2020.

Applications

The TGA receives approximately 800 licence and certificate applications every financial year. In the 2019–20 financial year there were 587 licence applications and 191 certificate applications for a total of 778 applications. These applications include initial applications for new licences or certificates, applications to vary manufacturing authorisations, applications to vary quality or production nominees or administrative details on the licences as well as re-inspection applications that are automatically generated according to the TGA's risk framework.

Table 1: Application types received in 2019–20

Application types received	Licences	Certificates
Initial applications	39 (7%)	93 (49%)
Re-inspection applications	135 (23%)	81 (42%)
Applications to vary	274 (47%)	N/A
Applications to revoke	9 (1%)	N/A
Applications to suspend	4 (1%)	N/A
Internal applications (GMP certificates, etc.)	126 (21%)	17 (9%)
Total	**587 (100%)**	**191 (100%)**

To support Australian industry we provide step by step instructions for submitting applications for Australian manufacturing licences and overseas GMP certification as well as instructions on how to revoke, suspend or vary a licence.

Inspection scheduling

We schedule GMP inspections according to the TGA's risk framework. All Australian manufacturing sites are inspected on a periodic basis, based on the product and manufacturing risk categories and the previous compliance rating of the site. Prior to March 2020, inspections were routinely scheduled in to a parcel every 6 months. However in response to rapid changes in type and urgency, this changed to a parcel every 2 months. This change will continue to be monitored to determine if there is a corresponding decrease in the processing time for applications for initial inspections of Australian and overseas manufacturing sites.

The inspection parcel may include initial inspections for new manufacturing sites, routine reinspections of licensed sites, inspections to increase the manufacturing scope of a licensed site and compliance triggered inspections.

Australian manufacturers

Table 2: Processing times for inspections of Australian manufacturers

Processing time	2018-19[a]	2019-20[a]
Initial inspections conducted within 3 months of application	16 (94%)	12 of 13 (92%)[a]
Re-inspections conducted within 6 months of due date	112 (75%)	82 of 117 (70%)[b]

a. For 2019–20, this processing time performance is based on the readiness of the manufacturer for inspection.

b. There were a total of 35 re-inspections which did not achieve the preferred 6 month processing timeframe. The majority of these inspections (23 of the 35 delayed inspections) were blood and biological manufacturers which were delayed due to inspector resourcing. The delays did not introduce any safety or quality risks. To address this issue an additional blood and tissue inspector will be recruited in the coming financial year and cross training of selected medicines inspectors will take place.

Overseas manufacturers

Table 3: Processing times for inspections of overseas manufacturers

Processing time	2018-19	2019-20
Initial inspections conducted within 6 months of application	21 (85%)	11 of 16 (69%)[a]
Re-inspections conducted within 6 months of due date	44 (85%)	20 of 28 (71%)b

a. For 2019–20, this processing time performance shown in this report is based on the readiness of the manufacturer for inspection.

b. There were a total of 8 re-inspections which did not achieve the preferred 6 month processing timeframes. These inspections were delayed due to inspector resourcing and/or travel security concerns. The delays did not introduce any safety or quality risks.

Inspections

Manufacturers of medicines and biologicals are regularly inspected by the TGA using a risk-based approach to ensure compliance with GMP standards.

Overseas manufacturers who supply medicines or biologicals to Australia are also required to manufacture therapeutic goods to the same high standard and are inspected by us. Where a recognised international regulator has approved a manufacturer, it may not be necessary for TGA inspectors to also inspect the same manufacturing site if an Australian sponsor intends to import and supply medicines from that site. These arrangements occur under the GMP Clearance program.

Inspections conducted

Australian manufacturers

Table 4: Outcomes of inspections

Compliance status (Australia)	2018-19	2019-20
Number of inspections conducted	195	163[a]
Satisfactory compliance (of completed inspections)[b]	152 (78%)	99 (60%)[c]
Marginal compliance (of completed inspections)[b]	29 (15%)	32 (20%)[c]
Unacceptable (of completed inspections)[b]	8 (4%)	5 (3%)[c]
Level of compliance under assessment at period end	6 (3%)	27 (17%)

a. The number of domestic inspections declined marginally in 2019–20 due to delays with COVID–19 and a short period of 6 weeks to revise our processes to accommodate a remote and hybrid inspection program.

b. For a description of compliance ratings refer to manufacturer compliance history.

c. Increases or decreases across compliance categories for a given year are a reflection of the reinspection timeframes for manufacturers due for inspection in the year. Reinspection timeframes are based on the compliance rating achieved at the last inspection. The data shows that 60% of manufacturers had a compliance rating outcome of satisfactory which included those with a compliance rating of A1 and A2. The marginal compliance rating was at 20% for those with a compliance rating of A3 and there were 3% with an unacceptable compliance rating.

Table 5: Breakdown of compliance status and type of manufacture

Compliance status	Type of manufacturer
Satisfactory	Biologicals, Blood, Sterile & Non sterile medicines, Listed medicines and Medical Gases.
Marginal	Biologicals, Sterile & Non sterile medicines, Listed medicines and Non sterile Active Pharmaceutical Ingredient (API).
Unacceptable	Radiopharmaceutical, Non sterile medicines and Listed medicines.

Table 6: List of domestic manufacturers with A1 compliance rating during 2019-20

Manufacturer name
Aussie Tucker Technik Pty Ltd T/A IJ Contract Pharmaceuticals
CSL Innovation Pty Ltd
SLHD Royal Prince Alfred Hospital Department of PET & Nuclear Medicine
T Cann Pty Ltd
DHL Supply Chain Australia Pty Limited
GlaxoSmithKline Australia Pty Ltd
THC Pharma Pty Ltd
Redland Pharmaceuticals Pty Ltd
Nestle Australia Ltd
Contract Pharmaceutical Services of Australia Pty Limited
Tasmanian Alkaloids Pty Ltd
Luina Bio Pty Ltd
DHL Supply Chain Australia Pty Limited
Antaria Pty Ltd (storage facility)
National Institute of Complementary Medicine
The Pharmaceutical Plant Company Pty Ltd
Aspen Pharma Pty Ltd

Manufacturer name
Pharmalytics Pty Ltd
Tasmanian Alkaloids Pty Ltd
BOC Limited
Australian Red Cross Lifeblood - An Operating Division of The Australian Red Cross Society
Saputo Dairy Australia Pty Ltd
CSL Behring Australia Pty Ltd
Acrux DDS Pty Ltd
Propharma Australia Pty Ltd
GlaxoSmithKline Consumer Healthcare Australia Pty Ltd
Eurofins Chemical Analysis Pty Ltd
Selborne Biological Services (Australia) Pty Ltd
Air Liquide Australia Limited

a. The list of manufacturers above with an A1 compliance rating accounts for all A1 outcomes from domestic inspections conducted during the 2019¬20 financial year. It does not include manufacturers receiving an A1 rating in previous years.

Overseas manufacturers

Table 7: Outcomes of inspections

Compliance status (overseas)	2018-19	2019-20
Number of inspections conducted	75	51[a]
Satisfactory compliance (of completed inspections)[b]	64 (85%)	31 (61%)[c]
Marginal compliance (of completed inspections)[b]	11 (15%)	13 (25%)[c]
Unacceptable (of completed inspections)[b]	0 (0%)	3 (6%)[c]
Level of compliance under assessment at period end	0 (0%)	4 (8%)

a. The TGA conducted fewer overseas GMP inspections due to travel restrictions associated with the COVID-19 pandemic. The last overseas inspections performed were in March 2020.

b. For a description of compliance ratings refer to manufacturer compliance history.

c. Increases or decreases across compliance categories for a given year are a reflection of the reinspection timeframes for manufacturers due for inspection in the year. Reinspection timeframes are based on the compliance rating achieved at the last inspection. The data shows that 61% of manufacturers had a compliance rating outcome of satisfactory (A1 and A2). The marginal compliance rating (A3) was at 25% and there were 6% with an unacceptable compliance rating.

Table 8: Breakdown of compliance status, country and type of manufacture

Compliance status	Country	Type of manufacture
Satisfactory	USA, India, China and France	Sterile & non-sterile medicines and Listed medicines
Marginal	USA, India, Canada and South Africa	Biologicals, sterile and non-sterile medicines
Unacceptable	USA and India	Sterile medicines and non-sterile medicines

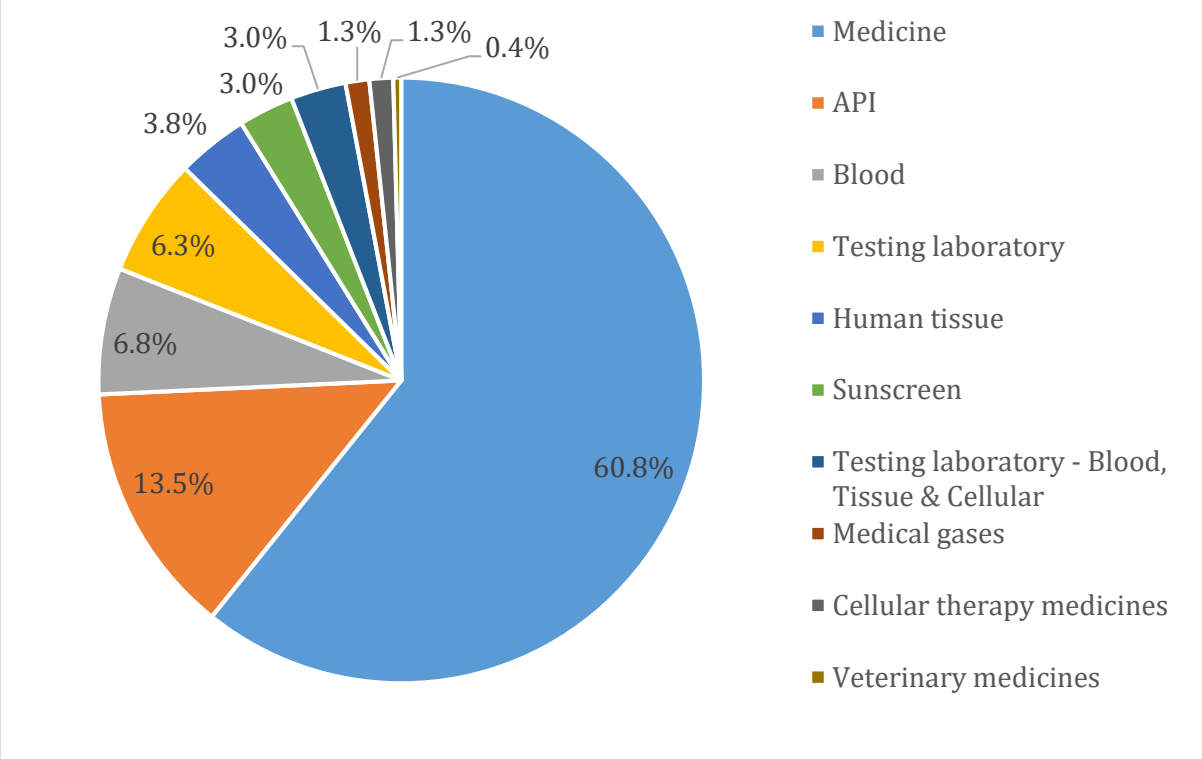
Table 9: List of overseas manufacturers with A1 compliance rating during 2019-20

Manufacturer name
Rubicon Research Private Limited
Medispray Laboratories Pvt Ltd
Jubilant Generics Ltd
BCM Cosmetique
Fluoromed LP
RPG Life Sciences Limited
Medreich Limited

a. The list of manufacturers above with an A1 compliance rating accounts for all A1 outcomes from overseas inspections conducted during the 2019¬20 financial year. It does not include manufacturers receiving an A1 rating in previous years.

Manufacturing types

Figure 1: Manufacturing Types for conducted Inspections



a. The majority of our inspections both domestically and internationally for the financial period 2019-20 were for medicines (60.8%), followed by API (13.5%), then blood (6.8%), testing laboratories (6.3%), human tissue (3.8%), sunscreens (3.0%), testing laboratory – blood, tissue & cellular (3.0%) and cellular therapy medicines (1.3%).

b. The represented medicines sector (60.8%) were comprised of non-sterile, sterile, listed, radiopharmaceutical and compounded medicines.

Common deficiencies

The following are the most common deficiencies observed during the 2019–20 financial year.

Table 10: Medicines manufacturers' common deficiencies

Area	Issue
Deviations	Poor investigations, poor root cause analysis No root cause analysis Poor correction and preventative action plan (CAPA)
Computerised system	Electronic system used for the quality management system processes was not validated Back up of data Audit trails Inadequate procedure and access control
Validation	Inadequate cleaning validation Poor process validation Poor equipment qualification

Table 11: Blood and Biologicals manufacturers' common deficiencies

Area	Issue
Deviations	Poor investigations
Environmental	Inadequate environmental controls specified Frequency of environmental monitoring
Validation	Poor validation identification Validation not performed to procedures, do not always demonstrate full control of the manufacturing process

Application outcomes

Australian manufacturers

The licence applications received in 2019–20 resulted in 23 new licences being issued.

Table 12: Status of manufacturing licence applications processed

Licence status (Australia)[a]	2018-19	2019-20
New licences granted	15 (47%)	23 (30%)
Withdrawn application	1 (3%)	45 (55%)[b]
Revoked licences – at request of licence holder	13 (41%)	10 (12%)
Revoked licences – TGA	0	0
Suspended – at request of licence holder	3 (9%)	3 (3%)
Suspended – TGA	0	0
Total	**32 (100%)**	**81 (100%)**

a. As at 30 June 2020, there were 259 Australian companies holding manufacturing licences covering 404 sites.

b. In previous financial years, the number of new applications withdrawn at the applicant's request were reported. The method of calculation has changed this year to include all applications withdrawn at the applicant's request.

Overseas manufacturers

Table 13: Status of manufacturing certification applications processed

Applications completed	2018-19	2019-20
Certified	83 (56%)	86 (54%)
Rejected[a]	66 (44%)	72 (46%)
Total completed	**149 (100%)**	**158 (100%)**

a. Rejections include withdrawn applications.

As at 30 June 2020, there were 187 overseas manufacturers covering 222 manufacturing sites that are subject to TGA inspection.

Compliance

Compliance signals

In 2019-20 the TGA have further developed the assessment of compliance signals for Australian manufacturing sites and foreign manufacturing sites that may import product for the Australian market. It is the responsibility of sponsors to report known compliance issues at their manufacturing sites and advise us of any regulatory actions by any competent authority for the manufacturing sites. Information on the expectations of sponsors is published on the TGA website.

Compliance signals received by us are assessed to determine the need for any further regulatory action. The types of information considered include regulatory actions by competent authorities for foreign manufacturing sites, recall actions, results of TGA laboratory testing, non-compliance identified at routine inspections as well as anonymous tips offs.

The compliance history of manufacturing sites and the products currently supplied by manufacturing sites are considered to establish a profile of the manufacturer. Sponsors may be asked to provide risk assessments to support the continued supply of products from manufacturing sites that are identified to have GMP compliance signals. This information is reviewed, together with the profile of the manufacturer, to determine whether regulatory actions are warranted. In 2019–20 there were 50 regulatory actions taken in response to GMP compliance signals:

- 25 inspections of Australian manufacturing sites included assessment of a compliance signal
- 9 inspections of overseas manufacturing sites were scheduled
- 1 unannounced inspection of an Australian manufacturing site was performed
- 13 GMP clearances were conditioned in response to a compliance signal
- 2 GMP clearances were suspended in response to a compliance signal.

Meetings with manufacturers

Licence application and variation

There were 9 meetings held between GMP technical specialists and manufacturers regarding reviews of facility plans and also determining the readiness for inspection. These included manufacturers for medicinal cannabis, biotechnology and biological products.

Poor compliance

There were 8 meetings held between GMP technical specialists and manufacturers due to poor compliance at inspection to determine ways forward for improving compliance. These included manufacturers for complementary medicines, radiopharmaceutical and biotechnology products.

GMP Clearance

Reliance

To reduce regulatory burden on Australian industry, the TGA's GMP Clearance framework leverages off GMP inspections performed by overseas regulatory authorities to avoid the need for us to conduct an on-site inspection for the same manufacturer.

Over 90% of all overseas manufacturer approvals are performed via the GMP Clearance Mutual Recognition Agreement (MRA) or Compliance Verification (CV) pathways, thus significantly reducing the amount of on-site inspections required and costs to industry associated with such activities.

There are more 2500 overseas manufacturers approved by the TGA following a GMP Clearance desk-top assessment.

Table 14: GMP Clearance manufacturer approval by location

Pathway	Manufacturer location	Percentage[a]
MRA	European Union and European Economic Area[b]	93%
	Canada	3%
	New Zealand	3%
	Singapore	1%
CV	India	43%
	United States of America	29%
	China	10%
	Japan	5%
	Taiwan	2%

a. Percentage figures have been rounded.

b. For the purpose of this report, manufacturers located in Switzerland have been included in the EU and EEA grouping.

The above table shows that the overwhelming majority of manufacturers approved via the MRA pathway are located in Europe whilst the remainder of our MRA partners only account for a small percentage of manufacturer locations.

For the CV pathway, India, the USA and China account for the largest proportion of manufacturer approval locations. There are several other countries that make up less than 2% of manufacturer approvals and the majority of these are PIC/S participating authorities.

Annual numbers

The number of GMP Clearance applications received and processed annually by us continues to remain at a high level. There was an increase of over 500 total applications received in the 2019–20 financial year.

Table 15: GMP clearance application status

Application status	2018-19	2019-20
Applications received	6628	7153
Applications completed		
Approved	6252 (88%)	6414 (91%)
Rejected	854 (12%)	637 (9%)
Total completed	**7106 (100%)**	**7051 (100%)**

Table 16: Number of GMP Clearance applications received and completed by type from 1 July 2019 to 30 June 2020

Table 15 GMP clearance application status, includes all types of applications submitted which can be further broken down into the following categories:

Application category	Applications received	Applications completed
Re-activate[a]	0	29
Cancel	8	8
Extend	2131[b&c]	2115
New	2352[d]	2363
Variation	2662b	2565

a. Requests for the re-activation of a GMP Clearance can only be made via email and not via the TGA eBusiness services portal. These types are excluded from total numbers of applications received.

b. The majority of application types received were to vary existing GMP Clearances. This includes changes in scope as well as renewal applications.

c. Extension applications increased from 1966 in 2018–19, which can be attributed to the impact of COVID-19 and the suspension of GMP inspections.

d. There were also a high number of new applications which may reflect new sponsor / manufacturer relationships being used for Australia. However, this also captures applications where sponsors don't renew or vary their GMP Clearance as per the published guidance but rather select to submit a brand new application.

Submitting a new application instead of a variation to your original GMP Clearance will break the link to your Australian Register of Therapeutic Goods (ARTG) record potentially requiring variations to be made.

GMP Clearance processing timeframes

The TGA re-introduced target processing timeframes for GMP Clearance applications submitted from 1st July 2019. These timeframes were agreed with industry following consultation with the TGA-Industry Working Group on GMP (TIWGG) and do not include applications where liaising is requested as part of the application submission or where GMP non-compliance signals have been received by other regulatory authorities.

Table 17: Target processing timeframes for GMP Clearances

Application type	Target processing timeframe	Percentage[a] completed within timeframe
MRA	30 working days	99%
CV Non-Sterile API	60 working days	99%
CV Sterile API	75 working days	99%
CV Non-Sterile FP	90 working days	98%
CV Sterile FP	120 working days	100%

a. Percentage figures have been rounded.

Incomplete and Not issued applications

We continue to see a high number of applications submitted where the required evidence is not provided for assessment. These applications result in a stop clock being applied which remains in place as they progress into the assessment queue. Sponsors will experience significant delays with applications where the required evidence is not provided for assessment.

We estimate that that over 15% of CV applications submitted are incomplete and remain that way moving into the assessment queue.

Table 18: Number of GMP Clearance applications actioned by pathway

Pathway	Applications received	Applications completed	Applications issued	Applications not issued
MRA	2710	2709	2581	128
CV	1472	1292	1190	102

- The number of applications that are not issued following a desk-top assessment remains relatively high. This is time consuming for both TGA and industry.
- For the MRA pathway generally the reason applications are not issued is due to the incorrect certificate being provided for assessment.
- For the CV pathway, the main reason applications are not issued is a lack of a reply from the Australian sponsor to provide the requested evidence.

Business improvement and education

As part of our commitment to continually review and improve our processes and guidance material, as referred to in the TGA Business Plan 2019-20, we made a number of improvements to our GMP program, supporting guidance material and presented at a number of educational events in the last financial year.

Health Canada evidence

In August 2019, following a pilot program with Health Canada (HC), we were able to amend our process for GMP Clearance applications using Health Canada evidence when HC performed GMP inspections outside their borders for the CV process. Previously, the HC exit notice alone was insufficient to facilitate a desk-top assessment outside the boundaries of the Australia-Canada MRA, potentially resulting in the need for a TGA on-site inspection to be performed.

Evidence of GMP for prescription medicines

In November 2019, following close collaboration with the product regulatory areas, we published an update to the evidence of GMP for prescription medicines guidance which was originally published in 2015.

This guidance update removed the need for GMP Clearances to be submitted for container sterilisation. This was a significant problem for industry for many years as these sites typically didn't have the evidence required for GMP Clearance.

GMP Clearance code tables guidance

In June 2020, following consultation with the TIWGG, we published the GMP Clearance code tables guidance. This addressed a longstanding gap for Australian sponsors by providing interpretation of manufacturing steps for GMP Clearance as well as guidance around navigating the TGA Business Services Code Tables and product lodgement validation rules.

Medicinal cannabis manufacture guidance

In late 2019, TGA published revised guidance on the GMP requirements for medicinal cannabis manufacture to clarify GMP requirements, so products come to market earlier and avoid any unnecessary delays in market authorisation. This GMP guidance was developed by inspection technical specialists working with the Office of Drug Control, Pharmacovigilance and Special Access Branch and also the Medicinal Cannabis Industry Association. Clarify the need to obtain a GMP Licences, so manufacturers could come to market in the most timely manner.

Education of Australian manufacturers

MQB is continuously looking at areas of our legislation, regulation, standards and/or guidance to see where we can improve understanding. To achieve this we presented at a number of events during the year. The topics ranged from validation, distribution and supply chain, microbiology deficiencies, data integrity, GMP requirements for medicinal cannabis and the most commonly identified deficiencies. In addition, expectations with the current PIC/S guide to GMP for medicinal products (PE0013) that was fully adopted on 1 January 2019 after a 12 month transition period. Updates on the planned implementation of PIC/S guide to GMP for medicinal products (PE0014) for 1 July 2020 were also presented in early 2020.

International collaboration

In keeping with TGA's commitment in the TGA Business Plan 2019-20 and International Engagement Strategy 2016-2020, to strengthen our regulatory programs through international engagement with comparable regulators MQB participated in the following working groups and undertook the following activities.

Inspection scheduling collaboration activities

The TGA participates in international information meetings with regulatory partners to share inspection planning information for Active Pharmaceutical Ingredient manufacturing sites. Foreign manufacturing sites of shared interest are identified and opportunities for joint inspections are explored to limit multiple inspections of the same sites. The monthly meetings also facilitate inspection reliance and harmonisation.

In addition, we are currently chairing a pilot programme for sharing inspection planning information for sterile finished dosage form manufacturers.

PIC/S meetings and working groups

On the international front, we presented on the revisions of Annex 1 for sterile medicines and Annex 2 for Advanced Therapeutic Medicinal Products (ATMP).

There were PIC/S arrangements put in place in the period 1 July 2019 to 30 June 2020 for:

- A new working group on cross contamination in shared facilities
- A new working group on cells and tissues.
- TGA became the PIC/S representative on the International Committee on Harmonisation (ICH) Working Group on the drafting of the new guidance on Q13 Continuous manufacturing to ensure harmonisation between the ICH and PICS guidance, as required.

Working groups

The TGA participated in, or led a number of international working groups.

Table 19: International working groups

Working group	TGA role
Sub Committee on GM(D)P harmonisation	Member
Sub Committee on Compliance	TGA is co-chair with Health Canada
Sub Committee on Strategic Development	Member
Expert Circle on Active Pharmaceutical Ingredients	Member
Expert Circle on Blood, Tissues, Cells and ATMPs	Member
PIC/S working group on Data Integrity and Data Management	TGA is the co-chair with MHRA
PIC/S working group on the Classification of Deficiencies	Chair
PIC/S working group on Annex 1	Member
PIC/S working group on Cross Contamination in shared facilities	Member
PIC/S working group on Annex 2	Chair
PIC/S working group on Cells and Tissues	Chair
ICH working group on Q13 Continuous manufacturing	TGA is representing PIC/S as an observer on the working group

New GMP requirements for medicinal products

In line with our commitment in the TGA Business Plan 2019-20, the TGA updated, and then in May 2020, provided notice that we would be adopting the current version of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* PE009-14, 01 July 2018 (PIC/S Guide to GMP), excluding Annexes 4, 5 and 14, as the manufacturing principles for medicines and active pharmaceutical ingredients, with effect from 1 July 2020. The PIC/S Guide to GMP is available from the PIC/S website.

GMP changes over time due to various reasons such as:

- providing guidance for the management of new technologies
- addressing gaps in existing compliance requirements
- managing risks identified through inspections and regulation
- facilitating continuous improvements in the way medicines are manufactured.

The TGA uses internationally harmonised manufacturing standards to allow manufacturers to operate in an international environment. The TGA maintains its GMP standards in line with updates issued through PIC/S. Regular updates are necessary to provide consistency and confidence of overseas regulators in the standards that are applied globally and to promote quality assurance of inspections. This also provides harmonisation of technical standards and procedures with international inspection standards for manufacture, testing and supply of medicines.

Australian manufacturers benefit from reduced regulatory burden where the TGA is able to adopt harmonised international standards and establish mutual recognition agreements and cooperative arrangements with comparable overseas regulatory authorities.

Compliance with the basic requirements of the PIC/S Guide to GMP has been expected since 1 July 2020; however, inspectors are taking a pragmatic approach to discussing and reporting deficiencies relating to any new supplementary requirements.

The TGA have provided a 12 month graduated transition period to allow manufacturers time to assess the new supplementary requirements contained in the new Manufacturing Principles and implement changes to procedures and practices to fully comply with the new guide.

Full compliance with the PIC/S Guide to GMP will generally be expected after this 12 month transition period ends.

We acknowledge the impact that the COVID-19 pandemic has and may have on the ability of manufacturers to adopt new supplementary requirements, and therefore the overall implementation period will be reviewed prior to the completion of the 12 month graduated transition period, to determine whether additional time is required.

The TGA participated in a range of industry consultations during 2019–20 with the TIWGG and will continue to work with industry to develop further interpretive guidance where required. Further details regarding TGA information sessions regarding the adoption of the new PIC/S Guide to GMP will be published on the TGA website.

Good Clinical Practice pilot inspection program

Background to the pilot program

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials. Complying with GCP helps to ensure that the rights, safety and well-being of clinical trial participants are protected and that the trial data generated are credible.

In line with TGA's commitment in the TGA Business Plan 2019-20 in the 2019–20 financial year, the TGA undertook a pilot programme of domestic GCP inspections to assess the feasibility for an ongoing programme of GCP inspections. A domestic GCP inspections program will support our ability to identify and manage risk under the clinical trial notification and clinical trial exemption schemes, and further enhance the reputation of Australian clinical trials for quality and integrity. An internationally aligned regulatory framework will support Australia's position in a competitive global clinical research market. A domestic regulatory GCP inspections program will strengthen Australia as an attractive clinical trial research destination for both the local medical technologies, biotechnology and pharmaceuticals sector, when deciding where to conduct their trials, and in attracting internationally sponsored clinical trials.

Clinical trials were selected for inclusion in the pilot from a list of organisations interested in volunteering for the pilot GCP Inspections Program received from the public consultation with stakeholders undertaken in January 2019. The pilot inspection programme included investigator sites/organisations, from different states across the country, commercial and non-industry trial sponsors, and both private and public clinical investigator sites. In addition the clinical trials selected for the pilot program were chosen to cover as many different trial types as possible, including the trial phase (phase 1 to 3), therapeutic area, different aspects of trial design (single versus multi-centre trials, trial population and trial complexity). The pilot program of voluntary GCP inspections was restricted to investigator sites of clinical trials involving pharmaceutical medicines.

The GCP inspections were performed according to procedures modelled on the published procedures for the conduct of regulatory GCP inspections in use by the European Medicines Agency with specific items verified by interviews, reviews of documentation and inspection of facilities.

Inspections included the review of the following:

- Legal and Administrative – examination of aspects related to the implementation, progress and termination of the clinical trial, including evidence of communication with the Human Research Ethics Committee and regulatory authorities.
- Organisational – examination of the implementation of the trial at the site, including qualifications and experience of site personnel, delegation of authority, standard operating procedures, facilities and equipment, source of the Investigational Medicinal Product (IMP), monitoring and auditing records.
- Informed Consent – determine whether patient consent was obtained in accordance with GCP Guidelines.
- Clinical Trial Data – review whether the trial was conducted according to the study protocol by source data verification, particularly inclusion/exclusion criteria.
- Management of the IMP used in the trial.
- During the 12-month pilot program a total of 7 GCP inspections were conducted. A further 3 inspections planned for the April–June quarter 2020 were cancelled due to the COVID-19 pandemic. The pilot inspection programme has been extended until December 2020 and will incorporate remote inspection processes for future inspections.

Stakeholder engagement

2019 GMP Forum

The TGA first hosted the annual industry GMP Forum in 2018 which is a conference designed to discuss a range of interesting and innovative topics covering different aspects of medicinal GMP and the regulation of medicines more generally. The Forum is of significant interest to industry personnel involved in the quality assurance, regulation, risk assessment and GMP of medicines, in addition to personnel working for medicine-based Small and Medium Enterprises (SMEs).

On Thursday, 21 November 2019, MQB hosted the TGA's second Industry Forum on GMP. This is the largest face to face event currently hosted by us, with 465 delegates in attendance on this occasion. The program included presentations by TGA experts on GMP clearance processes, common inspection deficiencies, data integrity in the laboratory and how the work of our laboratories intersect with GMP requirements.

Industry presenters gave presentations on Pharma 4.0 and building a GMP compliant culture, and other sessions focused on emerging technologies and products such as faecal microbiota transplantation and medicinal cannabis. The day concluded with an interesting panel session offering advice on how to participate in successful GMP inspections. In addition to the formal presentation sessions, there was a 'café area' where delegates could visit our GMP, recalls, SME Assist and Office of Drug Control staff throughout the day. Presentations from the day are available on the TGA website.

TGA Industry Working Group on GMP

The TIWGG facilitates consultation between the TGA and the industry on regulatory matters relating to GMP. Amongst other relevant issues, the TIWGG provides a mechanism for us to seek comments from the Australian industry on the revision, development and application of PIC/S guidelines.

The TIWGG usually meets 3-4 times per year and its broad membership comprises representatives nominated by 11 peak industry associations representing medicine sponsors and manufacturers.

The current members of the TIWGG are:

- Accord Australasia
- Active Pharmaceutical Ingredient Manufacturer's Association of Australia (APIMAA)
- Australia and New Zealand Region of International Society of Cell and Gene Therapy (ISCT)[1]
- Australia New Zealand Industrial Gas Association (ANZIGA)
- Australian Red Cross Lifeblood (Lifeblood)[1]
- Biotherapeutics Association of Australasia (BAA)[1]
- Complementary Medicines Australia (CMA)
- Consumer Healthcare Products (CHP) Australia
- Generic and Biosimilar Medicines Association (GBMA)
- Medicinal Cannabis Industry Association (MCIA) 1
- Medicines Australia (MA).

[1] Following TIWGG's establishment in 2014, these four peak industry associations were added to the working group's membership in May 2020.

During 2019–20, 4 TIWGG meetings were convened on 17 October 2019 (meeting #18), 26 March and 2 April 2020 (meeting #19), 23 April 2020 (meeting #20) and 13 May 2020 (meeting #21). Due to COVID-19 related restrictions, the 2020 meetings were convened via video- and teleconference.

Further information about the TIWGG, including its terms of reference, membership, meeting summaries and technical working groups is also available on the TGA website.

Responding to COVID-19

To ensure the ongoing supply of quality medicines, blood and human tissue products from Australian and overseas manufacturers, TGA undertook a broad range of activity to help ensure the continued operation of Australian manufacturers. This activity ranged from:

- prioritisation of applications for manufacture
- addressing supply issues (e.g. by enabling the treatment of cancer in public and private hospitals nationally)
- adapting our approach to the conduct of inspections of manufacturers to help ensure their continued operation
- providing information to government on the manufacture of therapeutic goods such as hand sanitisers
- contributing to work intended to address medicine shortage issues.

Key activities undertaken

- On 2 May 2020, TGA approved an amendment to the *Therapeutic Goods Regulations 1990 Schedule 7, Part 3-3* to exempt certain radiopharmaceuticals and radiopharmaceutical active ingredients (RAI) to enable specified persons, within public and private hospitals and public institutions without a manufacturing licence, to manufacture radiopharmaceuticals or RAI for the treatment of a patient in another state or territory. This exemption addressed the current difficulties in obtaining supplies of radiopharmaceuticals and RAI from a licensed manufacturer in a timely manner during the COVID-19 pandemic.
- TGA developed new arrangements to allow continued and flexible oversight of GMP at licenced domestic manufacturing sites during the COVID-19 pandemic.
- In March 2020, following the Prime Minister's announcement for all Australians to reconsider their need to travel internationally, TGA reviewed all planned overseas inspections. In line with international regulators all international inspections were postponed until further notice. Affected sponsors were contacted about this decision, which did not affect supply of critical medicines. In response, the TGA developed new arrangements to allow continued and flexible oversight of overseas manufacturers by performing remote GMP inspections.
- TGA were also conscious that a number of our overseas regulatory partners faced disruptions to their on-site inspection programs for both domestic and overseas manufacturers. This has created additional challenges for our existing reliance mechanisms requiring similar flexibility in our regulatory oversight. In order to support industry, we implemented a temporary change to our documentation requirements for GMP Clearance applications submitted through the CV pathway during the COVID-19 pandemic, enabling sponsors to provide:
  - a recently expired inspection report from a recognised regulator, and
  - a GMP Clearance questionnaire as well as any additional documents identified during the completion of the questionnaire.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Manufacturing Quality Branch	November 2020

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