



“Navigate GMP with DBA”*

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REGULATORY AGENCY INSPECTIONS OR AUDITS –

Fact: Regulatory agencies make unannounced inspections of therapeutic goods manufacturing facilities. Be prepared for them to ensure that the process goes smoothly. Would you be ready if an FDA investigator or TGA Inspectors or Investigators arrived today,?

Inspections are most successful if they are non-confrontational.

You should develop a written inspection procedure. Don't be complacent, a badly handled regulatory inspection can cost you more than time and money! Staff should be trained because the SOP is only effective if all staff know and follow it when confronted with the stress of an inspection. Key staff should know how to handle announced and unannounced inspections, avoid alarm and ineffectiveness and know exactly what each persons actions in the inspection process. All staff (including reception and security), not just the inspection team, need to be trained on how to be inspected.

One of DBA core business activities is to organise mock inspections to identify and correct key weaknesses in GMP compliance!

Regulatory agencies such as the TGA and the US FDA have broad authority to inspect any facility that manufactures, processes, packs or stores therapeutic goods. “Facility” also has broad definitions and includes vehicles such as trucks and planes. The inspection does not need a warrant. Inspectors or Investigators must be granted access to the manufacturer’s production facility where “compliant products are fabricated, assembled, tested, stored, and shipped”. Regulatory agencies may have authority to enter licensed premises (at a “reasonable time” within reasonable limits, and in a reasonable manner) or public or private property connected with an activity governed by a permit or regulation¹. “Reasonable” depends on the circumstances. For example, a midnight inspection may be reasonable if the factory is working at that time. However, it may be possible to request a delay in the inspection until the key staff can reach the factory because it is not reasonable for example for a night shift supervisor to be asked technical questions beyond their competence. Proceeding with the audit or inspection without proper representation could result in unnecessary misunderstandings and conflicts.

¹ Therapeutic Goods Act 1989 **40 Conditions of licences** (4) In addition to any conditions imposed under subsection (1) or (2), each licence is, except as otherwise specified in the licence, subject to the conditions that the holder of the licence will: ... (b) allow an authorised person: (i) to enter, at any reasonable time, the manufacturing premises to which the licence relates; and (ii) while on those premises, to inspect those premises, any therapeutic goods manufactured at those premises and processes relating to that manufacture, and to take samples of goods of that kind and, with the agreement of the holder, to take photographs of those premises, goods or processes; and (c) where an authorised person enters premises as mentioned in subparagraph (b)(i), require the holder or his or her employees at those premises to answer questions relating to procedures carried out at the premises; and (d) if requested to do so by an authorised person: (i) produce to the person such documents relating to the manufacture of therapeutic goods manufactured at those premises as the person requires and allow the person to copy the documents; or (ii) produce to the person for examination any batch samples kept by the holder; and (e) comply with such other conditions (if any) as are specified in the regulations for the purposes of this section.

On the other hand, in Australia there is no mention of “reasonable time” in relation to “searches for the purpose of checking compliance with the Therapeutic Goods Act”.

Regulatory agencies with powers of entry include the US FDA, the TGA, Environmental Protection, Water Authorities, Occupational Health and Safety, Fire, etc. Inspections may be conducted for a number of reasons including regular scheduled visits as provided for by the agency inspection procedures, or as a response to employee or community complaints, non-compliance activities, investigation of defects reported by regulatory laboratory or as a method of establishing compliance in support of a licence application.

CAN: An FDA Investigator or TGA Inspectors or Investigators generally may inspect facilities that engage in the manufacture of therapeutic goods, all vehicles used to ship or hold product, all relevant equipment, finished and unfinished materials, containers, labeling, all records required by applicable good manufacturing practices or quality systems regulations, records, files, papers, notebooks, computer records, processes, quality controls, quality assurance and facilities, and anything relevant to whether therapeutic goods are contaminated, adulterated or misbranded. TGA may also require personnel to answer questions and produce records.

CANNOT: An FDA Investigator or TGA Inspectors or Investigators generally cannot inspect financial or sales data (other than shipping records), pricing data, personnel data (other than information regarding the qualifications of technical and professional personnel), most research data. A hot topic is internal audit reports. FDA may only check records demonstrating that the audits were conducted in accordance with the company's schedule, but not minutes of management review under 21 C.F.R. § 820. 20(c), but may see the records submitted to management for the review. See 21 C.F.R. § 820.180(c); 820.100(a)(7). TGA may request any records relating to the steps of manufacture. It could be held this includes internal audit reports.

TGA may not be allowed to inspect non-therapeutic goods (such as food, confectionary, cosmetics or toiletries) and therapeutic goods that are for animal use only and not for human use, unless by consent.

Inspections typically have four phases, (1) an orientation, a walk-through of the work areas, then (2) the fact finding phase with records review, sampling, and personnel interviews, etc, (3) a caucus for report writing and (4) an exit meeting.

The Regulatory representatives may take measurements, or make tests. Some agencies may have the power to take samples, seize goods or seize equipment, including hard and “soft” records, and collect evidence that may be used in court proceedings.

Check the relevant legislation on the internet now. For example all Australian legislation is at <http://scaleplus.law.gov.au/browse.htm>

Do this now!

Every year write to the inspecting agency to give it the company's designated contact person's name and phone number (who should know all the manufacturing and quality processes, and trained in managing inspections), company hours and holidays, company safety and health entry rules (including any training and qualifications necessary for entry to controlled environments such as clean rooms), safety supplies the Regulatory representatives should bring if required if relevant (eg safety glasses, steel capped safety shoes, etc), and medical requirements (eg TB

testing if entry to BCG vaccine manufacturing or animal house, rabies immunisation if inspecting rabies vaccine manufacturing, etc).

Provide staff including reception and security staff a list of key contacts to be notified when Regulatory representatives arrive. Identify at least one key contact and alternate within the company who would be responsible for immediately notifying individuals within the organisation of the inspection. This contact list may include: Laboratory and Production Staff, Security, Legal, Public Relations, Senior Management, Quality Assurance Unit. Identify the Inspection walk-through team up front. Include who should be notified after the inspection of the results.

When the Regulatory representatives arrive unannounced

On arrival: Reception or security staff must check the Inspectors' or Investigators' identification. Normally they will have photo id. Copy it. Check by phone back to their office if you are suspicious or if it is outside of normal hours. There are instances of attempts made to gain forced entry with fake ID. Record names, addresses and telephone numbers of the inspector. Get a business card. Remember no id, no entry. Have a policy on observers accompanying inspectors – it is wise to not permit observers to regulatory inspections on the pretext of training – staff will be under considerable pressure without also having to answer questions from trainees.

Ensure you have a person delegated at all times to answer questions and accompany the inspectors. They must have training and be well-informed about the manufacturing activities.

Notification: Notify the relevant managers that an inspection is in progress. If necessary have a contact person who can respond quickly.

Immediate Preparations Arrange translators if necessary. Designate a contact person to manage the inspection. Arrange for a meeting room for the Regulatory representatives. Set up close by a company “debrief” room with computers and debriefing staff because you should as soon as possible get written reports from everyone who has spoken to or escorted the inspectors. Nominate at all times a contact officer to stay in the debrief room. The debriefing reports should detail who, what, when, where and how the inspection was carried out. In particular the reports should detail any suspected non-compliances so that immediate analysis and corrective action can be commenced – don't wait for the formal report to start corrective action! Identify key people to coordinate the audit and ensure they are familiar with all systems, key responsibilities, practices and records.

Pre-inspection or Opening Meeting: Before commencing the inspection activities, request a meeting to determine the nature and extent of the inspection. Ask the Regulatory representatives to describe the purpose of the visit, the information that they want to get, and the reason for the inspection. Request an agenda for the inspection. If possible limit the scope of the inspection to that agenda. Get the following information from the Regulatory representatives - What is the nature of the visit?. if a compliance inspection – what specific areas do the Regulatory representatives want to visit? What does the Regulatory representatives wants to see during the visit. What departments should be present at the opening meeting, inspection, inspection and exit meeting? How long will the inspection take? What information will be available at the exit meeting and after the inspection meeting? Find out if the Regulatory representatives want to speak with a qualified person about a technical issue, review records, visit manufacturing or laboratory areas to verify compliance.

Explain the company policy on photographs and video recordings, and sound recording, and that an escort will be provided at all times while on the company property. You should also give them a written notice of your company's policies on photographs, sound recording and your copyright on all documents and intellectual property. You should be able to provide a current copy of the organisation chart, Site Master File, site map with process, personnel and product flow, recent changes in the facility, staff changes since last visit, corrections or responses to issues noted at the last inspection, recent correspondence with the inspector's office. Request that if there are any suspected or actual non compliances noted that they be identified to the team as soon as it is seen. Some Regulatory representatives do not do this but wait until the exit meeting.

Briefing on Health, Safety and related matters: If possible at the opening meeting provide a briefing for the Regulatory representatives on health and safety to ensure your procedures are followed. For example, tell them (even if they have visited the site before) about safety equipment, hygiene requirements, jewellery (including wristwatches), makeup, medical status requirements, identification badges, gloves, garments, hard hats, safety shoes, hearing protection, etc. You may indicate training and practical qualification is required for entry to classified areas, such as clean rooms or areas where hazardous or potent drugs are manufactured or tested, or where there may be eg radiation sources. You should not assume any prior training has been adequate or will meet your company requirements.

If relevant, indicate areas where hypoallergenic material such as betalactams are made and that if the Regulatory representative is allergic entry could be life threatening. You can ask them to sign a form declaring allergic conditions but they may refuse to sign it. Tell them if there are areas where entry is barred if a person is suffering from certain contagious diseases, skin conditions (such as dermatitis, eczema, or psoriasis), or conditions such as chronic rhinitis, or upper respiratory tract conditions.

You could reasonably refuse entry where you think there is a safety risk such as confined spaces (such as tanks), or hazardous areas, eg cytotoxics drugs production, high voltage, radiation. If the Regulatory representatives insist on entering critical areas without training and or proper safety equipment or with proscribed medical conditions, and have the legal power to do so, do not obstruct them but make a written report of the training refused or objectionable medical condition, etc, and then be prepared to reject material being made there. You may need to requalify the room after inspection.

And if the Regulatory representatives refuse the safety briefing at least provide them with a documented procedure on health and safety issues, and what you expect a reasonable person should do to take care of the quality, safety and efficacy of products on your premises. Record any refusals.

The inspection

Company Inspection Team: Form a team which will be the company's main interface with the inspector or investigator. At least three people are needed for each inspector, investigator or inspection team – as escorts, rapporteurs (or scribes), and contact person. The inspection team will be responsible for developing a working relationship with the inspector, will document each day of the inspection and will ensure that the Regulatory representatives receives or is denied (carefull!) access. Consequently, all must be knowledgeable about the Law, facility, products, guidelines and regulations. Because the inspection can be an unannounced the inspection team

should be ready at all times. If a non compliance is being noted, the inspection team needs to know the law and be prepared to separate out for discussion purposes what is the Law, Policy/Guidelines, Best Practices, and what is Opinion. The team can have a member who is expert or a consultant if it choses. In these cases the Regulatory representative could ask the consultant not to answer questions on behalf of the company. In extreme cases the team should have legal counsel accompany it to assist with interpretations on the Law, and to advise whether questions asked are material to the inspection. There is nothing to prevent the expert or legal counsel giving advice during the inspection providing it does not obstruct the inspection process.

Escort: always escort! Accompany the Regulatory representatives at all times during tours, personnel interviews, records reviews and sampling activities. The escort is the closest link to the inspector. Visitors should not be allowed to wander around unsupervised. The escort should be responsible for gathering requested information, review all requested documents, sort out irrelevant or privileged information, submit information to the inspector, keep a record of all requests by the Regulatory representatives and commitments made by the company. The escort should schedule and attend all interviews and meetings. Ensure all requests from the Regulatory representatives go through the inspection team, and limit where appropriate the inspector's access to only the relevant records, facilities, and materials that are subject to inspection. If a question cannot be answered by the escort then a responsible person in the company should be located to provide the answer

Rapporteur or scribe. Appoint one! Appoint one for every team. Have them take comprehensive notes. They are not to provide answers to questions as their only duties should be to note times, areas, what was asked, what answers were given, where the team was, SOP reference numbers, document details, what was photographed etc. In the event of a dispute, their notes and report will be crucial.

Introductions: Ensure others in you company are aware of the inspection, and the focus of the inspection. Introduce them as an eg "Inspectors or Investigators from ABC agency inspecting the QC laboratory testing procedures"

Questions: Remember: Inspectors or Investigators are experts in conducting inspections. Respond to the inspector's questions honestly, frankly, and openly. And concisely - only answer the question - provide only the information that is requested because the Regulatory representatives will tell you if more information is needed. If you don't know the answer to a particular question, say so but commit to provide the answer from someone who does know the answer

Interviews: Inspectors or Investigators may wish to interview personnel to verify for example training has been provided, to verify operator competency, to determine if established procedures are being followed, or for other purposes relevant to the inspection. In some circumstances the investigators or inspectors may wish to tape record or video tape the interview. In all of these cases ensure legal counsel is present and ensure a translator is available if the questions are not in the person's native language.

Records: Start a file for the inspection. Keep in it the record of the inspectors' ID, name and office telephone numbers, documents reviewed and copied, and attendees at the opening and closing meetings. Keep a daily log of areas that were inspected, employees who participated, dates and times when the Inspectors or Investigators were on site, names of all employees interviewed, the inspection focus during the day, the questions and answers, the documents

copied (and make a second copy for your own records), any samples collected, and the tone of the inspection. Keep a record of all requests by the Regulatory representatives and commitments made by the company.

Mark any photocopies you are asked to provide as “Uncontrolled”, “Commercial in confidence” or “Confidential”, © Copyright of XYZ (with the date), Copying by any means prohibited, “Proprietary Information”, etc. It is a moot point but you do not have to provide photocopying facilities, and if you do, then you could reasonably recover the costs. Make sure copies provided to the Investigators or Inspectors are accurately labelled and record them on a form. Request a receipt from the Regulatory representatives for all copies. The receipt should indicate that they are aware of the proprietary and confidential nature of any copies they have received.

Create a register of all the copies.

Photographs Regulatory representatives may wish to examine or photocopy records, or photograph processes or conditions that they observe during the inspection. If your procedures forbid photography say so but be aware the regulations may allow the Regulatory representatives to take photographs.

Can the Regulatory representatives take photographs or videos during an inspection? Maybe.

For FDA it is unsettled. For TGA, they can only take photographs with your agreement but if it is a search “of certain premises to monitor compliance with Act”², if it is for the purpose of collecting evidence of criminal activity and the entry to the premises has been lawfully made or made with a warrant then TGA can take photographs, videos, sketches, copies of records, etc. In this case make sure you take your own photographs as well and obtain your own set of the Investigator’s or Inspector’s photos for later review. If an Inspector or Investigator is taking photos; you should take photos. It is important to consider taking an occasional photo that includes the Investigator or Inspector. Take photographs of corrected items if relevant for the company response.

² 1989 Therapeutic Goods Act **46A Searches of certain premises to monitor compliance with Act**

(1) An authorised person may, subject to subsections (2) and (3), and to the extent that it is reasonably necessary for the purpose of finding out whether this Act or the regulations have been complied with, enter premises to which this section applies and do any of the following: (a) search the premises and any thing on the premises; (b) inspect, examine, take measurements of, or conduct tests (including by the taking of samples) concerning, any thing on the premises that relates to therapeutic goods; (c) take photographs (including video recordings) or make sketches of the premises or any thing on the premises; (d) inspect any book, record or document on the premises.

(2) An authorised person must not, under subsection (1), enter premises that are a residence unless:

(a) the occupier of the premises has consented to the entry; or (b) the premises are used for commercial purposes in relation to therapeutic goods, in addition to residential purposes.

(3) An authorised person is not entitled to exercise any powers under subsection (1) in relation to premises if: (a) the occupier of the premises has required the authorised person to produce his or her identity card for inspection by the occupier; and (b) the authorised person fails to comply with the requirement.

(4) This section applies to: (a) premises of a person: (i) who has been granted an approval or authority under section 19; or (ii) who has been granted an approval under section 19A; or

(iii) in relation to whom therapeutic goods are registered or listed; being premises connected with the importation, export, manufacture or supply of therapeutic goods, or the keeping of records relating to the importation, export, manufacture or supply of therapeutic goods; and (b) premises to which the person in relation to whom therapeutic goods are registered or listed, or the sponsor of the goods, must allow access as a condition of the registration or listing of the therapeutic goods; and (c) premises in relation to which a licence has been granted under Part 4 for the manufacture of therapeutic goods, or premises at which records are kept in relation to such manufacture.

Attitude: You should have a policy to competently and proactively participate in any regulatory inspection. Be Professional. Do not be argumentative, don't lose your temper and don't get angry. Be Polite. Be courteous. Be Pleasant. Be Responsive. Be Cooperative. Be Patient. Be Positive.

Be aware of your body language – eg “closed/back” (folded arms, chair pushed back from the table) is negative, “open/forward” (circle arm towards inspector, chair forward) is positive. Don't make fists, or point or wag fingers! Stay calm.

Try not to respond to comments, but only answer questions. These will usually start What (... if the you have a reject?), Why (... is this tool here?), When (... do you carry out maintenance?), How (... often do you revalidate the autoclave?), Where (... is the distribution record ?), Who (... is in charge of engineering?), and Show me (the risk analysis and validation protocol). If comments are made such as “I put it to you that the operations are not in control”, or “I put it to you the operator is not trained”, immediately arrange a written positive response to correct any misunderstandings. If necessary, politely disagree if appropriate. Inspectors or Investigators must be also be flexible, resourceful, and sometimes pragmatic to make the whole process work

Responding to Questions Listen carefully. Answer only the questions asked. Tell the facts as you know them. Don't speculate - Don't joke. Don't try to tell the Regulatory representatives what you think they might want to hear. If you don't know the answer to a question, say so - be precise, but commit to provide someone who can answer the question as soon as possible. Never answer questions starting with vague phrases or words such as “Usually, “Generally speaking”, “I think we do ...” or worst still “To be honest with you ...”. Listen to the inspector's question completely before answering. If you are not sure you understand a question say so, or repeat the question back in your own words. “I think you are asking me “.....? Is that correct?” When asked to describe what you do or how you do it, don't guess, get the applicable SOP, open it up and use it. Never mislead and don't try to hide information, or lie! The Regulatory representatives are not consultants! Do not ask the Inspectors or Investigators for advice! if appropriate, clarify what is acceptable so as to reach agreement and resolve the non-conformance

Samples: Regulatory representatives may wish to take samples. Ensure you obtain receipts for all samples taken and obtain or take a duplicate sample yourself. If possible get a duplicate sample from the inspector. In some cases, the Regulatory representatives may have to pay or arrange payment for the sample. Note the amount on the receipt.

Analyses: If samples are taken and analysed on the spot, request copies of sample analyses. . Depending on the specific analysis, results may be available either during or after the inspection. This information may or may not be provided upon request, depending on the nature of the sampling and agency policy.

Suspected Non-compliance: It is recommended that any suspected non-compliance issues be appraised immediately. As soon as possible and before the inspection is over if possible provide a root cause analysis (using formal deductive methods such as Failure Mode Effect Analysis, Ishikawa Fault Tree Analysis, or Causal Tree Analysis), a Risk Analysis and a Corrective Action Plan. If you can correct immediately before the closing meeting then do so but any changes must be formally assessed using your change control procedures, but make sure any necessary re-training and re-validation is completed before you restart. Simple corrective actions can be completed during the inspection. Make sure you document everything and make sure that any

corrective action completed against a non-compliance that was resolved during the inspection is properly noted by the Regulatory representatives in the written report. Be prepared to clarify any issues by knowing the guidelines, law and understanding the spirit of the law completely. Be aware that regulators in response to major non-compliances usually are looking for corrective action AND preventative action, not just correction.

If you feel that the proposed non-compliance is not warranted, discuss the issue thoroughly. Review the area of concern and recognise that if you do not take the time to explain your manufacturing or quality process, the Regulatory representatives may not understand it, and may not realise that you are following the relevant GMPs. However, they may come to a better understanding if you have good knowledge and explanations showing that the manufacturing process is in control and meets relevant laws and guidelines.

Closing meeting

Hold a closing meeting at the end of the visit to review the Inspectors' or Investigators' findings. It is recommended that the closing meeting be attended by senior management. Consider routinely including your Legal section. They lend expertise to discussions and will help distinguish between regulations and policies as well as mediate differences of opinion as to interpretation. Discuss any findings with the Regulatory representatives and be sure to have explained any non-compliances *not* raised previously. Review the findings in enough detail to understand the issues – do not be rushed at this stage. Some Regulatory representatives will try to hurry through this stage eg by virtue of train or plane schedules. But take time to explain your manufacturing processes related to any issues, and how you comply with the law or guidelines. If discussing the issues know what is Law, Policy, Guidelines, Best Practices and Opinion. If the meeting is cut short arrange for a soonest follow up meeting.

Ask the Regulatory representatives to provide a written list of findings, with particular attention to issues or areas that the Regulatory representatives have found to be in actual or possible non-compliance. Ensure that you record these findings. Do not make any admission, conclusion or judgment regarding the compliance status of the finding yourself. Ask if additional actions or correspondence will take place and the schedule for any follow up actions, decisions, or information development. Make a commitment to resolve non-compliances in the agreed-upon time frame.

If, after discussing the issue with the Regulatory representatives, you cannot resolve any issues, initiate a dispute resolution process. If there are threats to your licence or its conditions in Australia, there will always be the appropriate appeal process to be followed in any written notice received. Know what it is and exercise your appeal rights if this required.

Review the inspector's report carefully; there could be errors. Object to any wording which is not neutral or is prejudicial. Non-compliances should be specific, objective, and factual, supported by evidence and should accurately reflect the relative risk. For example "SOP 123 did not state the name of the detergent or the dilution to be used in cleaning XYZ equipment" is acceptable but "SOPs were poorly written" is vague and lacks transparency; in which case seek clarification and evidence.

Determine if you will or will not sign the report. If you do sign make sure you add a comment that you are not indicating that you agree with the conclusion.

Regulatory Reports: Request that the Regulatory representatives provide a copy of their report for your records. Ask if you may review a draft copy of the report. This information may or may not be provided upon request, depending on Agency policy. In Australia, you have access to any information on your file and to the inspector's notebook under Freedom of Information. In some circumstances this is free of charge.

Thank the Regulatory representatives at the end of the meeting, don't forget they have a job to do and are usually very well qualified and expert.

Contacts: Ensure that the Regulatory representatives know who to call for further information regarding the inspection, and for exchange of additional correspondence.

Company Inspection Report and Response: Write summaries, reports for the records and responses immediately, or as soon as possible after the completion of the inspection visit, while the details are still fresh in peoples' minds. The company report should detail the inspecting agency, Regulatory representatives' names, nature and purpose of the visit, areas inspected, records reviewed or exchanged, sampling activities and results, personnel interviewed, detailed list of the personnel that the Regulatory representatives interviewed, areas of the facility visited by the inspector, information provided and inspection findings as provided by the inspector, and details of the opening and closing meeting. Keep a duplicate of any records that were photocopied for the Regulatory representatives and photographs that are taken. Keep the record for at least five years.

Corrective action: Soonest action needed!. You do not need to wait for an official letter or report to start any corrective action that may have been necessary.

DBA can provide specialist training on advanced GMP matters, including root cause analysis (using Causal Tree, Fault Tree, and Ishikawa techniques), risk analysis (using Failure Mode and Effect Analysis, and Failure Mode and Criticality Analysis), and conduct GMP gap analysis to determine compliance and regulatory risk. Check www.navigategmp.com for more information.

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