Institute for Standardization and Control of Pharmaceuticals

Quality Manual
Good Manufacturing Practice (cGMP) Pharmaceutical Inspectorate
For Medicinal Products

SOP no. QM-01/02

Page 1 of 34

Supersedes version - 01

Institute for Standardization and Control of Pharmaceuticals

Quality Manual
Good Manufacturing Practice (cGMP) Pharmaceutical Inspectorate
For Medicinal Products

SOP no. QM-01/02

<table>
<thead>
<tr>
<th>Name</th>
<th>Job Function</th>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mimi Kaplan, Ph.D.</td>
<td>Director, Institute for Standardization and Control of Pharmaceuticals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rami Kariv, Ph.D.</td>
<td>Head of GMP Inspectorate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarah Covrigaro</td>
<td>Quality Assurance Manager</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table of Contents

<table>
<thead>
<tr>
<th>No.</th>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>General</td>
<td>3</td>
</tr>
<tr>
<td>(ii)</td>
<td>References</td>
<td>4</td>
</tr>
<tr>
<td>1.</td>
<td>Scope</td>
<td>5</td>
</tr>
<tr>
<td>2.</td>
<td>Definitions</td>
<td>6</td>
</tr>
<tr>
<td>3.</td>
<td>Administrative Requirements</td>
<td>7</td>
</tr>
<tr>
<td>4.</td>
<td>Independence, Impartiality, Integrity</td>
<td>8</td>
</tr>
<tr>
<td>5.</td>
<td>Confidentiality</td>
<td>9</td>
</tr>
<tr>
<td>6.</td>
<td>Organization and Management</td>
<td>10</td>
</tr>
<tr>
<td>7.</td>
<td>Quality System</td>
<td>15</td>
</tr>
<tr>
<td>8.</td>
<td>Personnel Training and Qualification</td>
<td>18</td>
</tr>
<tr>
<td>9.</td>
<td>Facilities and Equipment</td>
<td>20</td>
</tr>
<tr>
<td>10.</td>
<td>Inspection Methods and Procedures</td>
<td>21</td>
</tr>
<tr>
<td>11.</td>
<td>Handling Inspection Samples</td>
<td>23</td>
</tr>
<tr>
<td>12.</td>
<td>Records, Documents and Data Controls</td>
<td>24</td>
</tr>
<tr>
<td>13.</td>
<td>Inspection Reports, Issue, Withdrawal of Licenses, GMP Certificates</td>
<td>25</td>
</tr>
<tr>
<td>14.</td>
<td>Sub-contracting</td>
<td>27</td>
</tr>
<tr>
<td>15.</td>
<td>Quality Improvement &amp; Corrective and Preventive Action (CAPA)</td>
<td>28</td>
</tr>
<tr>
<td>16.</td>
<td>Quality Audits</td>
<td>29</td>
</tr>
<tr>
<td>17.</td>
<td>Complaints and Appeals</td>
<td>30</td>
</tr>
<tr>
<td>18.</td>
<td>Periodic Review, Quality Indicators and Statistical Techniques</td>
<td>31</td>
</tr>
<tr>
<td>19.</td>
<td>Liaison with the Institute Laboratories</td>
<td>32</td>
</tr>
<tr>
<td>20.</td>
<td>Co-operation</td>
<td>32</td>
</tr>
<tr>
<td>21.</td>
<td>Handling Suspected Quality Defects and Rapid Alert System</td>
<td>33</td>
</tr>
<tr>
<td>22.</td>
<td>Publications</td>
<td>34</td>
</tr>
</tbody>
</table>
(i) General

The numbering of this quality manual is designed to address each of the sections in the document EN 45004, General Criteria for the Operation of Various Types of Bodies Performing Inspection, as well as integrating the body of the content of the PIC/S document "Recommendation on Quality System Requirements for Pharmaceutical Inspectorates" PI 002-3, September 2007.

This manual documents the Israeli Ministry of Health GMP Inspectorate's Quality System. The manual is intended to demonstrate that the GMP Inspectorate has the ability, integrity and resources to perform those activities required of it, as defined in the manual. The manual also addresses procedures for maintaining the quality system, including audits and periodic, formal review of quality indicators.

The activity described in this manual is covered by approved Standard Operating Procedures (SOPs) that provide precise instructions on how to perform and document the relevant activity.
(ii) References

This Quality Manual is based on the following normative standards and references. The content of the manual is intended to comply with the spirit and current understanding and interpretation of the referenced documents.

1. EN 45004: 1995, European Standard
   General Criteria for the operation of various types of bodies performing inspection

2. PIC/S, Pharmaceutical Inspection Co-operation Scheme

3. Compilation of Community Procedures on Inspection and Exchange of Information
   EC/EMEA 2006
1. Scope

The scope of this Quality Manual covers all those activities that fall under the responsibility of the GMP Inspectorate at the Ministry.

The Pharmaceutical Division of The Ministry is responsible for ensuring the safety, efficacy and quality of therapeutic goods supplied in Israel. The Pharmaceutical Division regulates finished pharmaceuticals (pharmaceutical products) and Active Pharmaceutical Ingredients (APIs) for human, biological and veterinary drugs. The authority for these activities is enacted in the legislation of the Pharmacists ordinance [New Version] 1981, Pharmacists Regulations (Medical Products) 1986, Pharmacists Regulations [Good Manufacturing Practice], 2008.

The scope of activities covered by the inspectorate includes:

- Human Pharmaceutical Drug Products
- Biological Pharmaceutical Products
- Plasma Products
- Veterinary Drug Products
- Active Pharmaceutical Ingredients (APIs)
- Pre-market approval for a new drug (innovative or generic) where it is determined that there is a need for inspection
- Approval for initiation of manufacturing of any of the above products in a new facility or site
- Approval for manufacture of Investigational Medical Products (Phase III)

The GMP inspectorate has at its disposal at any time, an up to date list of approved manufacturers inspected periodically by the inspectorate.
2. Definitions

Quality System The sum of all that is necessary to implement an organization's quality policy and meet quality objectives. It includes organizational structure, responsibilities, procedures, systems, processes and resources.

Quality Indicators Selected data intended to be periodically observed to assist in assessing trends in performance.

Israeli GMP Inspectorate The national body responsible for co-ordinating and carrying out pharmaceutical GMP inspections of pharmaceutical manufacturers, issue or withdrawal of Manufacturer's authorization and GMP certificates, providing advice and handling suspected quality defects.

Authorization For the purposes of this document, an authorization is defined as "Manufacturer's authorization" issued by the Ministry of Health according to Pharmacists Regulation (Good Manufacturing Practice) 2008 that provides authorization to manufacture medicinal products.
3. Administrative Requirements

The Institute for Standardization and Control of Pharmaceuticals (here and after referred to as "The Institute") is a part of The Pharmaceutical Division of the Israeli Ministry of Health and is responsible for enforcement of current Good Manufacturing Practice (cGMP) regulations in Israel. The General Director of the Israeli Ministry of Health confers the legal authority for supervision of pharmaceutical facilities and issuing certificates of compliance with cGMP upon the Director of the Institute for Standardization and Control of Pharmaceuticals. This is administered through application of the General Director's directive 15/03. The GMP Inspectorate (The Inspectorate) is an independent unit functioning within the Institute and reporting to the Institute Director.

The Inspectorate's activities and guidelines as how to implement these functions are documented together with a detailed description of the scope of activity for which it is competent in approved Standard Operation Procedures (SOPs). The Quality Manual is available to the general public on the Ministry of Health's website. The precise scope of each inspection or related activity is determined by the nature of the work involved and is determined in writing prior to initiation of the inspection based on review of relevant documentation.

The Inspectorate's liability is assumed by the State of Israel in accordance with national laws. The Inspectorate is part of the Ministry of Health and as such provides inspection services to the Ministry of Health. As such reporting requirements and work assignments are governed by applications made by companies to the Ministry of Health and / or ongoing GMP compliance activities in accordance with the Inspectorate’s Standard Operating Procedures.
4. Independence, Impartiality and Integrity

Every effort shall be made to ensure that activities of the Israeli cGMP Compliance Inspectorate are not compromised by conflict of interest or improper influence. The Inspectorate is an independent organization with no financial dependence on those institutions that are inspected by the Inspectorate. Inspectorate personnel shall be free from any commercial, financial or other pressures, which may affect their judgment. Procedures shall be in place to ensure that persons, companies or organizations external to the Inspectorate cannot influence the results of the inspections carried out by the Inspectorate.

The Inspectorate shall be impartial when performing an assessment of suitability for GMP requirement. In this regard, Inspectorate personnel are required to comply with the official conduct requirements of the Public Service Act. The decision on whether or not to issue a manufacturer's authorization and/or GMP certificate shall be based solely on documented, professional considerations resulting from observations and/or other evidence collected during the performance of the suitability assessment.

The cGMP Inspectorate may not provide consulting services to GMP authorized/approved clients, or to clients seeking GMP authorization/approval. Likewise, the cGMP Inspectorate may not make recommendations regarding particular vendors, consultants or other service providers beyond a general statement that they consider a company may require the assistance of a certain type of provider.

The Inspectorate may participate in regular meetings with various industry representative groups. Such meetings shall be open to all representatives of the particular group and shall preclude any influence on the issue of GMP or quality certification. Such meetings may be held in order to obtain industry input prior to policy making. However, at the end of the day the policy will be determined based on the Inspectorate's professional judgment and after a survey of current industry and regulatory practice.
5. Confidentiality

The confidentiality of commercial information shall be respected at all times. The Inspectorate shall ensure the confidentiality of information obtained in the course of its inspection activities and related duties. Proprietary rights and intellectual property rights shall be protected and respected.

Where appropriate access to commercial information shall be restricted to those persons within the Inspectorate that require said information for the performance of their professional duties. Such information shall be stored in restricted access areas. Likewise, personnel will make every effort to protect information stored in electronic format or on magnetic media or in any other computerized format.

Every public servant is required to sign on a confidentiality agreement as a condition for entering public service. This agreement requires them to maintain confidentiality of any information that comes to their knowledge in fulfillment of their public duties.
6. Organization and Management (Management Responsibility)

Organization
The organizational chart of the inspectorate is provided below. The Head of the GMP Inspectorate reports directly to the Director of the Institute. Inspectors report directly to the Head of the Inspectorate. Expert inspectors are usually managers in other units of the Institute, reporting to the Institute Director. When participating in an inspection team they report directly to the Head of GMP Inspectorate.
Management Responsibility
The Director of the Institute is responsible for the overall management of the GMP Inspection program and as such, for the overall management of the GMP Inspectorate.
The Head of GMP Inspectorate is directly responsible for management of the Inspectorate. If absent from the office for an extended period of time, responsibility for the management of the Inspection shall be delegated to another suitably qualified member of the Inspectorate. The authority for such delegation will be documented in the person's job description. In such an event, the Acting Head, GMP Inspectorate will be responsible for all inspection related activities for which the Head is normally responsible.
Based on his / her professional discretion, the Head, GMP Inspectorate, may delegate responsibility for specified activities to other Inspectorate personnel. The responsibility for making certain decisions may be delegated to specific review panels, the composition of which is determined by on an ad hoc basis. When a responsible person is absent from work and responsibility for a particular activity has not been formally delegated, delegation shall automatically be upwards, i.e. to the person's supervisor etc.
The Director of the Institute is reporting to The Director of the Pharmaceutical Division, who in turn reports to the Deputy General Director of the Ministry.
The responsibilities and authority of Inspectorate personnel are described in written job descriptions for each position in the Inspectorate. Job descriptions are signed by the staff member and by the Director of the Institute, indicating that they are both aware and agree to the scope of activities described therein. Job descriptions are filed in each staff member's personal file held by the Institute's personnel department.
Inspectorate personnel must have appropriate educational qualification, training and experience or suitable combination of these factors to enable them to perform their duties. Generally minimum educational requirements are for an academic degree in a life science (e.g. biology, microbiology, immunology etc.), pharmacy or chemistry. Practical experience in the pharmaceutical or related industry at a management level is considered an advantage although is not necessarily a pre-requisite for employment in the Inspectorate.
The inspectorate is currently staffed by the Head of GMP Inspectorate, GMP Inspector, 5 part time experts, QA Manager and supported by administrative staff of the Institute. The Inspectorate is located in the Givat Shaul neighbourhood close to the entrance to Jerusalem.

The responsibilities of the Director include but are not necessarily limited to:
- Overall management of the GMP Compliance Inspectorate
- Serving as the management representative for the Quality System
- Ensuring the availability of adequate resources for implementation and maintenance of the Quality System
- Intervening and assisting in resolving ongoing compliance issues where resolution between the Inspectorate and industry has not reached an acceptable conclusion
- Setting Policy for the requirement from the industry and standards of the Inspectorate
- Liaison with other regulatory and certification bodies, including PIC/S
- Liaison with industry representatives and bodies where appropriate
- Ensuring availability of adequate resources such that the inspectorate can conduct their activities in a professional and orderly manner
- Decision on deferral or rejection of Quality Certificates of medicinal product, Manufacturer's authorizations or GMP Certificates.

The responsibilities of the Head, GMP Inspectorate include but are not necessarily limited to:
- Setting policy for, ensuring and overseeing Quality Assurance of all activities performed by the GMP Compliance Inspectorate
- Ensuring the existence of and implementation of an annual training schedule as well as evaluating requests for training
- Arranging, planning and conducting inspections in Israel and, where required, abroad documenting inspections
- Approval of authorizations and certificates: recommending the issue, deferral or rejection of manufacturer's authorizations or GMP Certificates.
- Ensuring impartiality of the inspection group such that the outcome of audits is not compromised by conflict of interest or improper influence.
- Handling complaints.
- Review and approval of SOPs and other documentation related to the activities of the Inspectorate as appropriate.
- Ensuring the performance of management reviews and providing solutions to ongoing or recurrent problems presented in said reviews.
- Providing limited advice to industry, and advice to other departments in the Ministry of Health.
- Participating in internal audits, for cause inspections etc.
- Participating on committees or panels as necessary.
- Assessing evidence of GMP for overseas manufacturers.

The responsibilities of the Quality Assurance Manager shall include:
- Establishing and maintaining the Inspectorate's Quality System.
- Establishing and maintaining an internal audit program.
- Establishing and monitoring Quality metrics regarding the effectiveness of the Quality System to The Institute’s management review and as a basis for continuous improvement.
- Establishing, maintaining and monitoring correction of items entered into the Quality System CAPA program.
- Ensuring that pre-approval and ongoing compliance inspections are performed in a timely manner.
Any decisions relating to rejection of an authorization application or the suspension of an authorization shall be made by the Director of the Institute.

Inspections that require a specialized knowledge shall be restricted to inspectors with that knowledge, or specialists, e.g. persons from the Institute laboratories may be included in inspection teams to provide professional advice.
7. **Quality System**

The primary purpose of the Quality System is to ensure that adequate quality standards are maintained in all of the Inspectorate’s functions and duties. The Quality System requirements for the Israeli GMP Inspectorate should include and address all activities involved in the GMP inspection process.

The GMP Inspectorate has a quality policy that defines and documents the objectives and commitment to quality. The quality policy is used as an educational resource and must be understood and followed by all personnel working under the Inspectorate’s authority.

7.1. **Quality Policy**

The quality policy of the GMP inspectorate is as follows:

- The Inspectorate is committed to maintaining high performance standards, meeting the expectations of the Ministry and the general public in safeguarding public health by ensuring the uninterrupted supply of safe and efficacious medicinal products.
- The Institute's GMP Inspectorate is committed to operating an effective quality system that complies with the PIC/S recommendations (PI 002-3, September 2007). The system shall be such that it enables the Inspectorate to maintain the capability to perform its technical functions satisfactorily.
- The Inspectorate will do all in its power to meet its quality goals and to protect and be deserving of its respected national and international reputation.
- The Inspectorate will define and document their responsibilities and reporting structure in written approved standard operating procedures.
- The Inspectorate understands, is familiar with and is committed to the principle of continuous improvement in all areas of activity and has procedures in place to ensure that areas of weakness are systematically identified and acted upon in a timely manner.
Inspectorate personnel should be familiar with the Quality Policy and committed to the following principles that are to be complied with in performance of any and all of their duties:

The Quality Policy of the GMP Inspectorate is as follow:

- Maintain integrity and impartiality.
- Be consistent in decisions and assessments.
- Be polite, respectful, firm, fair and just.
- Respect the rights of all persons with whom they have contact during the performance of their duties.
- Maintain strict confidentiality of privileged information.
- Undertake continuous professional development, ensure that they are updated and aware of changes in standards, current practices and technologies and participate in appropriate training so as to ensure that inspectional standards are state-of-the-art.

7.2. **Documentation System**

The quality system is documented in a comprehensive set of Standard Operating Procedures (SOPs), of which, this quality manual forms an integral part.

One of the main procedures in the quality system is the Documentation and Change Control policy. This SOP ensures that only current, approved copies of controlled documents are available to all relevant personnel. Changes in controlled documents are reviewed and approved by relevant functions within the organization and result in re-issue of the document to all concerned persons with appropriate re-training. Where changes are made in a document there is a method for identifying changes from the previous version where such exists. The master copy of any superseded document is archived for a pre-determined period and all other copies are withdrawn from use in a timely and controlled manner.

As part of the documentation policy, there is a procedure for maintaining records relating to the activities of the GMP Inspectorate. The system should include any relevant documents including those received from authorization applicants and authorization holders where appropriate. A system to ensure the confidentiality of commercial information and intellectual property must be implemented and strictly maintained. Where required, records will be shared under the exchange of information procedures and arrangements between National...
Pharmaceutical Inspectorates and Mutual Recognition Partners, bearing in mind that the confidentiality requirements are incumbent on such partners and arrangements. Records must be handled in a manner that ensures they can be retained for a pre-determined period of time, consistent with any legal requirements and in such a manner as to provide prevent any damage or loss.

7.3. Internal audit
As part of the quality system internal audits are routinely performed in accordance with an approved procedure to verify compliance with this manual, with the Ministry's Inspection Manual and with the Inspectorate's SOPs. Internal audits are intended to verify the effectiveness of the quality system and may be performed by the Quality Assurance representative or by an appropriately qualified, independent, external auditor, in which case the auditor’s credentials will be maintained on file.
Where discrepancies or deviations in the quality system or performance of inspection are identified, either as the result of internal audits, complaints from the public or any other source, a Corrective and Preventive Actions (CAPA) procedure is in place to ensure that the non-conformity is registered, appropriate actions taken and follow-up performed to ensure that the actions are implemented and to measure their effectiveness.

7.4 Management Review
Management review is performed at least annually to review the quality system and ensure its continuing suitability and effectiveness. The results of the reviews are documented and followed up, including the setting of quality goals for the immediate future. Subsequent reviews address the implementation or failure thereof, of the goals determined at the previous review.
8. Personnel Training and Qualification

The GMP Inspectorate has a sufficient number of permanent personnel with the necessary expertise to carry out the volume and range of work demanded by its defined functions and duties. Personnel responsible for inspection must have appropriate qualifications, training, experience and knowledge of cGMP requirements, guidelines and expectations to enable them to perform the inspection and review functions required of them. This includes knowledge of the technologies used for manufacturing pharmaceutical products, of the methods of use of the products and of problems that may arise, including injury or harming of public health as a result of failure to meet the regulations. Personnel must understand and be fully conversant with the consequences of deviations that occur or may occur during the production, distribution or use of these products.

The authority for supervision of pharmaceutical facilities and issuing certificates of compliance with cGMP is conferred upon the Director of the Institute by the General Director of the Ministry of Health. The GMP Inspectorate is a part of the Institute reporting to the Director. A pre-requisite for joining the GMP inspection team is a scientific background. All inspectors have a relevant academic degree as a minimum requirement.

Staff responsible for inspection must have, apart from the above mentioned qualifications, the training and experience, as well as a satisfactory knowledge of the cGMP regulations and requirements for the inspections to be conducted. This includes understanding current interpretation of the requirements as they pertain to specific operations and product types. Personnel are expected to have the ability to make professional judgments as to conformity with the requirements based on inspectional findings and to prepare detailed reports based on those findings.

Inspectors are provided with on-the-job training including participating in training courses provided by foreign inspectorates as well as training courses provided by industry experts. As part of their training experience, inspectors may participate, as observers in GMP inspections conducted by FDA and European agencies in Israeli facilities. All
inspectors undergo a probationary period during which time they are apprenticed to a more senior inspector and are gradually permitted to be more active in the conduct of an inspection until the senior is satisfied that they are competent to perform the inspection unaided. Most inspections are performed by two inspectors. All inspectors are appointed and qualified by The Director of the Institute to conduct GMP compliance inspections. Inspectors must have relevant knowledge of the manufacturing technologies and product processes for the types of products being inspected, including understanding the methods of use of products and potential defects that may arise as a result of poor quality (safety and / or efficacy). The significance of deviations must be understood.

The inspectorate has a documented training system to ensure that the training of its personnel, in the technical and administrative aspects of the work in which they will be involved is kept up to date in accordance with its policy.

The training required is tailored to the ability, prior work experience and qualifications of the individual. Stages of training include:

- Induction
- Supervised working period with experienced inspectors
- Ongoing training and continuing professional development throughout employment to keep pace with developing technology and changing guidelines.

Records are maintained for each inspector, of academic or other qualifications, training and experience.

As part of their training, personnel are provided with guidance (SOPs) for their conduct as government employees protecting the public health.

Where necessary in order to perform their job function, personnel are provided with training in specific areas of activity.
9. **Facilities and Equipment**

The inspectorate has suitable and adequate facilities and equipment to permit them to perform their duties. Access is restricted to authorized personnel in assigned areas. Where appropriate there are written operating instructions and SOPs for use of the facilities.

Where computers are used there are procedures to ensure that the software is suitable for use. Operating procedures are in place to protect data integrity and to ensure that there are routine and regular back-ups of data. There are procedures for securing data from tampering and for maintenance of computers and automated equipment.
10. Inspection Methods and Procedures

The Pharmaceutical Inspectorate conducts repeated inspections of manufacturers as needed and in compliance with the Inspectorate’s SOPs. Inspection reports are issued in accordance with the PIC/S and the EMEA requirements.

All instructions, standards, written procedures, worksheets, checklists and references are maintained up to date at all times and are readily accessible to personnel. Where more than one inspector is involved in an inspection (which is generally the case), a lead inspector is always appointed to co-ordinate the inspection. The inspection report is prepared with input from all participants but is reviewed and finalized by the lead inspector. All participants sign off the report to attest to the accuracy of the content therein.

Inspection report format must comply with the PIC/S procedure. Reports are sent to the senior management. All inspectors who participated in the inspection should be involved in assessing the adequacy of the response that is subsequently received from the inspected company.

The inspectorate uses methods and procedures for inspection based on the EMEA and PIC/S procedures. There are SOPs for planning inspections and addressing inspection techniques including collection of samples where deemed appropriate. Inspections must be documented and any data collected during the inspection must be filed in a timely manner to ensure the integrity of such information. Usually inspectors will take a bound prenumbered notebook with them on inspections and record all observations directly into the notebook. The observations recorded in the notebook will be typed to the computerized inspection report. Inspectors could type the observation directly the laptop during the inspection. Copies of documents collected during inspection should be referenced in the notebooks and filed for ease of retrieval.

The inspectorate has a system for control of documentation such that all instructions, standards, guidelines, SOPs, check lists and references required to perform their duties are
maintained up to date and are readily available to all personnel.
The inspectorate has a system in place that ensures that all work undertaken by the organization is within the scope of the expertise of the personnel involved and that there are adequate resources available to perform the work in a professional manner.
Wherever the services of the inspectorate are required e.g. GMP inspections, the Director of the Institute is responsible for ensuring that any special conditions relating to a particular assignment are fully understood and available in writing. Instructions issued to staff must be unambiguous to enable them to perform their duties as required. The Director regularly reviews work being undertaken by the Inspectorate and where necessary corrective action is taken to rectify incomplete or ambiguous inspection findings, test results or unclear reports.
Where necessary, the Director may intervene with respect to sanctions imposed on companies failing to meet schedules for corrective actions or failing to commit to an adequate course of corrective action after an inspection that uncovers major findings.
The Director holds overall responsibility for ensuring that completed work is reviewed to confirm that the requirements are met.
There are SOPs addressing safety concerns related to performance of inspections and testing.
11. Handling Inspection Samples

There are SOPs in place for the collection, storage and handling of samples that are collected by the Institute to minimize the likelihood of damage or deterioration as a result of improper handling prior to testing. Samples collected for testing at the Institute laboratories must be carefully labeled and identified to ensure that the chain of custody is documented and maintained and to avoid any confusion regarding their identity. Any abnormalities must be recorded prior to testing such samples and if there is any doubt as to the suitability of the item for inspection or it does not conform to its description, this should be documented, a deviation report filled and the Head of the Inspectorate consulted as to whether the test should proceed.
12. Records, Document and Data Controls

A documentation control policy exists, signed by the Head of the GMP Inspectorate and by the Director of the Institute which addresses control of policies, procedures, instructions and guidelines. Likewise a record-keeping SOP addresses how records are maintained, filing systems (hard copy and computerized) for maintaining data so as to comply with legal and professional requirements. Record keeping is considered of paramount importance to the integrity of the work of the inspectorate. Records must contain sufficient information to support inspection findings and to permit satisfactory evaluation of the inspections. The record keeping procedure addresses records archiving of quality documents so as to ensure that hard copies of documents as well as electronic data are safely stored for the specified period in a secure location and protecting the confidentiality of the data.
13. Inspection Reports, Issue, Withdrawal of Authorization & GMP Certificates

The inspections performed by the GMP Inspectorate are covered by a detailed inspection report, based on documented inspection findings made in the inspector's notebook. The inspection report includes all the observations as well as background information addressing those systems and documents that were reviewed and personnel interviewed as part of the inspection. The report also documents precisely the names of the inspectors, the dates of inspection and the precise name and street address of the company audited.

The report, where it makes observations of deficiencies will be supportable by relevant legislation and/or guidelines such that any finding that is challenged by a company can be demonstrated to be justified. Inspectors will avoid the use of indiscriminate language and generalizations and will record findings in their reports using actual examples of observations from the audit. Words such as "all", or "no" or "numerous" should be avoided and quantification such as "at least X instances of...were observed" should be used.

Inspection reports must be signed by the inspector(s) and once issued may not be changed. Where it comes to the inspector's notice, after issue that there is an error in a report, a signed dated addendum should be issued.

The GMP Inspectorate should establish and maintain a system for the issue and withdrawal of Authorization and GMP certificates. Authorization and GMP certificate applications should be assessed and a determination of suitability made in a timely manner. Where time limits are imposed, inspection schedules should be adapted so as not to cause undue delay resulting in exceeding the time frames.
Where adverse inspection findings or complaints or other reports of serious non-conformities come to the notice of the Inspectorate regarding the holder of the Authorization or the holder of a GMP certificate, there should be a documented system for taking appropriate action to redress the situation. The system includes description of actions available to the inspectorate and may include suspension or revocation of the Authorization and/or GMP certificate. There is also a system for verifying that the concerned company complies with such actions when imposed. The system allows for appeals and the procedure is defined in an approved SOP.
14. **Sub-Contracting**

The GMP Inspectorate does not use the services of sub-contractors for performing inspections or for review of the quality part of applications. Should such practice be considered at any time in the future, appropriate SOPs will be written and approved, including qualification of the sub-contractor prior to entering into a contract with them. Such contract would require quality elements to be included, with clearly defined deliverables, up-front.
15. **Quality Improvement, Corrective & Preventive Action (CAPA)**

The GMP Inspectorate should establish and maintain a system of quality indicators, organized and defined in an approved Standard Operating Procedure. In particular these indicators should address, although not necessarily be limited to: timeframes for performing inspections, for issuance of reports, for review of submitted information, documentation, response to external or internal complaints, amount and quality of training provided to personnel and efficacy of the CAPA program (see below) including the internal audit program.

The Quality Assurance representative of the Inspectorate is responsible for maintaining a Corrective and Preventive Action (CAPA) program in accordance with the relevant SOP. The procedure requires entering any CAPA item into a computerized database with a target date for implementation of the required actions and an assigned staff member responsible for the implementation. The computer is programmed to provide an alarm several days prior to the implementation date to ensure timely follow up. Where CAPA items are not resolved by their implementation date, a new date is assigned and if this date is also not met, the item is brought to the attention of the Director of the Institute and the Head of the GMP Inspectorate at the next management review meeting.

CAPA items may result from internal or external audits of the Inspectorate, from complaints from the public or from industry or from deviation reports or change control items or as a result of any other quality related activity that identifies deficiencies in the functioning of the Inspectorate.

Management review meetings will include a review of recurrent CAPA items – those deviations that apparently have not been adequately resolved so that permanent solutions can be put forward and implemented.
16. Quality Audits

The Inspectorate has a procedure that requires performing internal audits. The purpose of these audits is to provide management with a picture of the state of compliance within the inspectorate to the Inspectorate’s Standard Operating Procedures and approved instructions. Furthermore, the audits assess compliance of the inspectorate with national and international standards for inspecting bodies including but not limited to international guidelines and ISO standards applicable to inspecting bodies (see references provided in this document).

Audits are performed at least annually by the Quality Assurance Manager or by an external, appropriately qualified consultant (CV must be maintained on file) and are documented in an audit report. On issuance of the report the Head of the Inspectorate must provide a written response with corrective actions and responsibilities within 30 days of the report’s issuance. On issuance of the response, a meeting is held with the Director of the Institute to discuss the findings and the suitability of the corrective actions. If necessary, an amended response is issued at the close-out of the meeting.

Corrective actions are entered into the CAPA program (see above) and follow-up is performed by the Quality Assurance Manager to ensure that target dates for implementation are met.

In addition to internal audits, the Inspectorate will undergo assessment by the PIC/S and/or European Community representatives. During such audits, if requested, findings of internal audits will be made available.

Internal audit findings are highly confidential and are not available to the general public. A document stating that audit findings were closed out may be made available if requested.
17. Complaints and Appeals

There is a written procedure for handling complaints registered by any party associated with an inspection. Irrespective of the nature of a complaint (professional, personal or otherwise) or the means by which it was communicated (telephone, fax, e-mail or letter), the complaint will be documented on a formal complaints form by the Quality Assurance Manager and will be investigated. A formal written reply will be made to the complainant stating investigation findings and corrective actions taken to avoid recurrence. The Director of the Institute must sign off all complaints.

Complaints are reviewed at least annually as part of the management review procedures and records are retained on file for a pre-determined time period in accordance with the approved Complaints SOP.
18. Periodic Review, Quality Indicators & Statistical Techniques

Management review meetings are held at least annually, to review quality indicators for the performance of the Inspectorate. An SOP is available describing the topics to be presented to management for discussion during the review.

An SOP addressing quality indicators, including but not limited to: amount and quality of training, number of inspections performed, time for reports to be issued, success of implementation of corrective actions to inspectional findings, number of deviation reports, number of complaints, number and severity of internal audit findings, number of open CAPA items and comparison of data with those from previous years.

Where applicable statistical techniques will be used to review quality indicators.
19. **Liaison with the Institute Laboratories**

The Inspectorate is maintaining defined liaison with the Institute's Laboratories in order to exchange information concerning the quality of medicinal products existing on the local market. SOP’s are available describing the sampling processes for starting materials and medicinal products as well as the transfer of information between the Laboratories and the Inspectorate.

20. **Co-operation**

The GMP Inspectorate is active in co-operation with other inspectorates throughout the world and in particulate with the PIC/S Pharmaceutical Inspection Cooperation Scheme. The GMP Inspectorate is concerned and interested in standardization of inspection activities and is committed to doing all within its power to forward such processes.

One of the main purposes of the Pharmaceutical Inspection Co-operation Scheme is to facilitate the exchange of information on national inspections in respect of the manufacture of medicinal products. The general requirements for National Pharmaceutical Inspectorates (the Israeli GMP Inspectorate is thus defined as a National Pharmaceutical Inspectorate) are to fulfill the requirements of National Legislation and of the relevant PIC/S guidance and documents. The specific obligations of the Israeli GMP Inspectorate are included in the quality system.

As an applicant to become a member of PIC/S, the requirements for the Israeli GMP Inspectorate are based on the PIC/S Recommendation on Quality System Requirements for Pharmaceutical Inspectorates, using the document as a reference and basis for developing and implementing a quality system appropriate to the scope, volume and range of work undertaken by the Israeli Inspectorate. This Quality Manual uses the PIC/S document as a
In accordance with the spirit of the PIC/S document, the Israeli Quality System is designed to establish and maintain an effective GMP Inspectorate to generate confidence within and between National Pharmaceutical Inspectorates in the assessment of compliance with current good manufacturing practice. By adopting a common standard for quality system requirements, it is intended to achieve consistency in inspection standards between National Pharmaceutical Inspectorates and thus facilitate mutual recognition of and confidence between these inspectorates. This common standard should help to facilitate the implementation of the PIC/S Joint Re-assessment Programme.

By using the PIC/S document as the basis for developing its Quality Manual and Quality System, inspection activities within the Israeli Inspectorate should be conducted according to a system that is compatible with other Participating Authorities.

The Israeli GMP Inspectorate will co-operate with PIC/s, the EU community and any or all of its associates in exchanging experiences in the maintenance and operation of quality systems.

21. Handling Suspected Defects and Rapid Alert System

The GMP Inspectorate should establish and maintain a system for handling of reports of suspected quality defects for licensed products. An approved Standard Operating Procedure addresses this topic and includes, where appropriate requirements for notification of the public and for recall if deemed necessary.

A system for Rapid Alert is addressed in the same procedure and requires maintaining an updated list of all product recalls from the marketplace.

The Standard Operating Procedure addresses liaison between the Inspectorate and District Pharmacists for the purpose of co-ordinating actions so as to guarantee rapid and efficient action in the case that there is the possibility of harm to public health.
22. Publications

The Pharmaceutical Inspectorate has an updated list of licensed manufacturers. The list is available to authorized bodies when request.

Version: 2
Date: JULY 2008
Changes from previous version:
1. Updated PIC/S PI-002 guideline.
3. New Israeli GMP legislation
4. New Manufacturer's authorization
5. Delete reference the business license
6. Allow recording of inspection finding directly to a laptop in additional to inspection notebooks.
7. Assessment of the inspectorate by the PIC/S and the EU committee, not by ISO certification body.
8. Internal audits final meeting is held with the Director of the Institute and not with the Head of the Pharmaceutical Division.