PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 021-2
25 September 2007

AIDE-MEMOIRE

GMP PARTICULARITIES IN THE MANUFACTURE OF MEDICINAL PRODUCTS TO BE USED IN CLINICAL TRIALS ON HUMAN SUBJECTS

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TABLE OF CONTENTS

1. DOCUMENT HISTORY

This Aide Memoire was developed by a team of PIC/S inspectors formed on a voluntary basis at the 2002 PIC/S Seminar in Montebello, Quebec, Canada.

Adoption by PIC/S Committee	13 September 2005
Entry into force	1 January 2006

2. INTRODUCTION

2.1 Investigational medicinal products (IMP) must be produced in accordance with the principles and guidelines of Good Manufacturing Practices for Medicinal Products. This Guide to PIC/S Annex 13 is to be applied in addition to the applicable GMPs. In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMPs to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. It is also intended to ensure that there is consistency between batches of the same IMP used in the same or different clinical trials, and that changes during the development of an IMP are adequately documented and justified.

2.2 The production of IMP involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, the need, often, for randomisation and blinding and increased risk of product cross-contamination and mix up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation, or, marketed products may be used which have been re-packaged or modified in some way.

2.3 These challenges require personnel with a thorough understanding of, and training in, the application of GMP to IMP. Co-operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products. The increased complexity in manufacturing operations requires a highly effective quality system.

2.4 The use of IMP may be an added risk to participating patients as compared to patients treated with marketed medicinal products, and therefore added assurance is required with respect to safety, quality and efficacy of IMPs.

2.5 This Aide Memoire has been based on PIC/S Annex 13, "Manufacture of Investigational Medicinal Products", (PE 009-2, dated 1 July 2004), for use by inspectors performing audits at manufacturing and packaging sites of medicinal products used in clinical trials on human subjects. Such inspections are relatively new in many countries, and take into account certain aspects of manufacturing and packaging which differ from those of marketed medicinal products. It provides for a standardized approach and provides a guideline for new inspectors in performing inspections at these sites.

3. PURPOSE

The purpose of this document is to provide guidance for GMP inspectors in the evaluation of sites that manufacture, package and label IMPs. This Aide Memoire is elaborated with the purpose of detailing the most specific and critical aspects that are necessary to be followed in an inspection with the objective of assuring compliance with the additional requirements specified in PIC/S Annex 13, at the site. It aims at maintaining a high standard of quality assurance and uniformity of approach among PIC/S member countries.

4. SCOPE

4.1 The scope of this document is to set at the inspectors' disposal, a working instrument to increase the performance in GMP inspections performed at a site that manufactures, packages and/ or labels medicinal products for clinical trials used on human subjects.

4.2 Using the field numbers of PIC/S Annex 13, (PE 009-2, dated 1 July 2004), stated in the left hand margin of this Aide Memoire, the inspector can refer to the specific wordings of Annex 13. The margins are adjustable for use in a landscape format thereby providing space for the inspector to insert the observations.

4.3 Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. These products do not fall within the definition of IMP. (refer to the Note under "Principle" in Annex 13).

5. REVISION HISTORY

Date	Version Number	Reasons for revision
25 September 2007	PI 021-2	Change in the Editor's co-ordinates

6. AIDE MEMOIRE

Text has been revised to correspond with PIC/S PE 009-2 (1 July 2004) “Guide to Manufacturing Practice for Medicinal Products”

PIC/S Annex 13 FIELD NUMBERS	TOPICS
QUALITY MANAGEMENT Fields # 1 and 2	Are Quality Systems described in approved written procedures taking into account GMP principles and guidelines applicable to IMP? Are there systems in place for documenting changes in product specifications and manufacturing instructions that provide for full control and traceability? State the SOP titles, reference numbers and dates of approval.
PERSONNEL Field # 3 & 4	Are all personnel involved with IMP appropriately trained in the requirements specific to these types of products? What is the level of training of personnel involved with IMP, specific to these types of products? Does the Authorized Person have a broad knowledge of pharmaceutical development and clinical trial processes? Provide a summary of his/her knowledge and experience.
PREMISES AND EQUIPMENT Field # 5,	What special measures are in place to minimize the risks of cross-contamination given the nature of the risks associated with these types of products? Does the design of the equipment and premises, inspection/ test methods and acceptance limits to be used after cleaning reflect the nature of these risks? Does the establishment produce under “campaign working”? For which products? Or is there dedicated equipment and self contained facilities? Are the choices of cleaning solvents based on the solubility of the product? Which are the cleaning solvents used and for which products?
DOCUMENTATION Specifications and instructions: Field # 6 and 7	Are specifications, manufacturing formulae, processing and packaging instructions, comprehensive, and updated promptly to the current state of the knowledge? How frequently are they re-assessed during development and are they promptly updated as necessary? How accurately does each new version take into account the latest data, current technology used, regulatory and pharmacopoeial requirements and does each version allow traceability to the previous document? State the titles and dates of written procedures used for incorporating changes. Do changes implemented address implications of product quality, such as stability and bio equivalence? Are rationales for changes recorded and the consequences of changes on product quality and on on-going clinical trials, adequately investigated and documented?

PIC/S Annex 13 FIELD NUMBERS	TOPICS
DOCUMENTATION Order Field # 8	Are all manufacturing, processing and packaging orders given by the sponsor to the manufacturer of the IMP, specifying the number of units and their shipping requirements? Are such orders always in writing (or transmitted by electronic means), precise enough to avoid any ambiguity? Are orders formally authorised and do they make reference to the Product Specification File and the relevant clinical trial protocol as appropriate?
DOCUMENTATION Product Specification File Field # 9	Is the Product Specification File (PSF), continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions? Are there written procedures for updating, with traceability to previous versions? State the title and approval date of these written procedures pertaining to maintaining the PSF Do these files contain specifics such as: specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product, manufacturing methods, in-process testing, approved label copy, relevant clinical trial protocols, randomization codes, technical agreements with contract givers, stability data, storage and shipping conditions? Is the information contained in the PSF used as the basis for assessment of the suitability for certification and release of a particular batch by the Authorised Person?
DOCUMENTATION Manufacturing Formulae and Processing Instructions Field # 10 and 11	Are there clear and adequate written instructions and records for every manufacturing operation? Are these records adequately detailed to facilitate preparation of the final version of the documents to be used in routine manufacture? Is the level of information contained in the PSF adequate to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping?
DOCUMENTATION Packaging Instructions Field # 12	Are the written packaging instructions adequately detailed given that IMP are normally packed in an individual way for each subject in the clinical trial? Do packaging instructions specify the necessary details such as: the number of units to be packaged, the number of units for quality control and retention samples? Do the written procedures specify product reconciliation to ensure that the correct quantity of each product has been accounted for at each stage of processing? Do the written procedures specify the line of documented investigative action when reconciliation expectations are not met?
DOCUMENTATION Processing, testing and packaging batch records Field # 13 and 14	Are batch records sufficiently detailed so as to accurately determine the sequence of operations? Do batch records contain relevant remarks which justify the procedures used and changes made and to enhance knowledge of the product and develop the manufacturing operations? Are there written policies to specify the duration for which batch manufacturing records must be retained, so as to comply with the periods specified in relevant regulations of that country?
PRODUCTION Packaging materials Field # 15	How detailed are the written specifications and the quality control checks to be conducted? What are the measures in place to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials?

PIC/S Annex 13 FIELD NUMBERS	TOPICS
PRODUCTION Manufacturing operations Field # 16, 17 and 18	Have critical parameters which were identified during development, been stated in writing? Have in-process controls which are primarily used to control the process, been identified in writing? Is due consideration by key personnel given to the key parameters, in-process controls, provisional production parameters gained from earlier development work and experience gained, in order to formulate the necessary instructions? Are the premises and equipment validated? List the protocol numbers and dates of the validation studies. For sterile products, are the sterilizing processes validated to the same extent as for sterile drugs authorised for marketing? Where required, is virus inactivation/removal and that of other impurities of biological origin, demonstrated to assure the safety of biotechnologically derived products? For aseptic processes, where the batch size is small, what is the number of units filled for validation using media fills? Does the number filled provide the desired confidence in the results obtained? For manual or semi-automated filling and sealing operations, is enhanced attention given to operator training and validating the aseptic technique of individual operators? Is it specified in written procedures? List the procedure numbers and dates of approval.
PRODUCTION Principles applicable to comparator product Field # 19 and 20	If the comparator product is modified, is data available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the comparator product? For re-packaged comparator product, has the “use-by” date been established, and has it been based on the nature of the product, characteristics of the container, storage conditions, and is it no later than the expiry date of the original package?
PRODUCTION Blinding operations Field # 21	What are the titles and dates of approval of written procedures to assure that : - the blind is achieved and maintained - allowance for identification of “blinded” products when necessary, including the batch numbers of the products before the blinding operation - possibility of rapid identification of the product, in an emergency Are these written procedures adequately detailed?
PRODUCTION Randomisation code Field # 22	How detailed are the written procedures to describe the generation, security, distribution, handling and retention of any randomisation code used for packaging investigational products and code-break mechanisms? What is the title and approval date of the written procedure? Are adequate records maintained?

PIC/S Annex 13 FIELD NUMBERS	TOPICS
PRODUCTION Packaging Field # 23, 24 and 25	What are the systems, procedures, specialised equipment, staff training, etc. in place to minimise the risk of product mix up during packaging which may require the handling of different products on the same packaging line at the same time? What are the preventative measures in place, such as label reconciliation, line clearance, in-process control by trained staff, to avoid mislabelling, particularly for "blinded" products which are similar in appearance? Are the specifications for packaging designed to protect the IMP during storage and transportation at intermediate destinations? What are the security features designed in the outer packaging so as to be tamper evident? How are storage and transportation conditions monitored? What is the title and date of approval of the written procedure?
PRODUCTION Labelling Field # 26 to 33	Do the IMP labels state all of the information listed in Field # 26 to 33, as they pertain to the regulations of the country in which the IMP will be used in clinical trials?
QUALITY CONTROL Field # 34 to 37	As processes may not be standardised or fully validated, what is the level of importance placed on testing to ensure that each batch meets its specification? Are all Quality Control functions being performed in accordance with the Product Specification File? Does Quality Control verify the effectiveness of blinding? What is the title and date of the written procedure? Are records of such evaluations maintained? Are samples of each IMP including blinded products, retained for the periods specified in the regulations of the country in which the IMP will be used? What is the title and date of the written procedure for retention of samples? Would the retained samples for each packaging run/ trial period enable conformation of product identity in the event of an investigation?
RELEASE OF BATCHES Field # 38 to 42	Are procedures established for the certification by the Authorised Person, that all relevant requirements have been met, prior to release of the IMP? State the title and date of approval, of this written procedure. Have there been any exceptions to these batch release procedures? Does the batch certification prior to release include the review of all records listed under Field # 40 of PIC/S Annex 13? Is packaging or labelling carried out at the investigator site, or under the supervision of a clinical trial pharmacist, or other health care professional? If so, does the sponsor seek the advice of the Authorised Person in this regard?

PIC/S Annex 13 FIELD NUMBERS	TOPICS
SHIPPING Field # 43 to 47	Is shipping of IMP conducted according to written procedures? Are these procedures in accordance with those given by or on behalf of the sponsor, as stated on the shipping order? Do IMP remain under the control of the sponsor until after completion of the two-step release procedure, as described under field # 44? Are both releases recorded and retained? Are de-coding arrangements made available to the appropriate responsible personnel before the IMP are shipped to the investigator site? Are detailed inventory of the shipments maintained by the manufacturer or importer? Do these records mention the addressees' identification? How frequently are transfers made of IMP from one trial site to another? Are there written standard operating procedures for this practice of IMP transfers. What is the title and date of the written procedure? Does suitability for transfer include a review of records? Is the product history while outside the control of the manufacturer, considered, such as review of storage condition monitoring records? Are re-labelling procedures available in writing and do these written procedures require that the Authorised Person certifies the release of the re-labelled IMP? Are re-labelling records retained and full traceability ensured?
COMPLAINTS Field # 48	Are the conclusions of all investigations pertaining to quality of the product shared between the manufacturer, importer and sponsor? Does it involve the Authorised Person and persons responsible for the relevant clinical trial, in order to assess any potential impact on the trial, product development and on subjects? What is the title and date of the written procedures for communicating the conclusions of investigations?
RECALLS AND RETURNS Recalls Field # 49 and 50	Are there written procedures for retrieving IMP and documenting this retrieval. What is the title and date of this procedure? Are these written procedures signed by the sponsor, manufacturer, importer? What are the titles and dates of these written procedures? Are the obligations of the investigator and monitor defined in these written procedures? Do the written procedures define the responsibility of the sponsor in ensuring that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the sponsor the need to recall any product supplied?
RECALLS AND RETURNS Returns Field # 51 and 52	Are IMP returned according to agreed conditions defined by the sponsor? Are these agreed conditions specified in written procedures? What are the titles and dates of these written procedures? Are returned IMP clearly identified and stored in an appropriately controlled, dedicated area? Are inventory records of the returned IMP maintained?

PIC/S Annex 13 FIELD NUMBERS	TOPICS
DESTRUCTION Field # 53, 54 and 55	Do written procedures clearly place the responsibility on the sponsor for destruction of unused and/or returned IMP? Do these written procedures specify that IMP should not be destroyed without prior written authorization by the sponsor, and only after discrepancies have been investigated and satisfactorily explained, and when the reconciliation has been accepted? Are delivered, used and recovered quantities of product recorded, reconciled and verified by the sponsor for each trial site and each trial period? Do the records of destruction operations account for all of the operations. Are records kept by the sponsor? When destruction of IMP takes place, is the sponsor provided with a dated certificate of, or receipt for destruction? Do these documents clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed?