CHAI Drug Quality Policy[1]

Overview

The Clinton HIV/AIDS Initiative (CHAI) is committed to ensuring the supply of high quality medicines. While CHAI appreciates that the vast majority of branded and generic drugs that have met the requirements for procurement by major funding agencies and procurement agents are safe and efficacious, it recognizes a continuing obligation to ensure product quality and performance.

CHAI plays several roles in the supply of critical medicines to developing countries, acting at times as a purchaser (e.g, through its UNITAID-funded Pediatrics or Second-Line HIV/AIDS Treatment Projects or when purchasing drugs in an emergency situation to address an imminent stock-out) or more commonly as a negotiator and facilitator of access to attractive pricing and other terms for drugs (e.g., when negotiating prices on behalf of the CHAI Procurement Consortium). In these roles CHAI takes both quality assurance (QA) and quality control (QC) measures. Quality assurance measures ensure that suppliers are able to meet quality standards. Quality control verifies that batches are manufactured according to quality standards on an ongoing basis. In some rare cases, CHAI may act purely as a "Negotiating Agent" on behalf of another global health organization. For example, CHAI is the Negotiating Agent on behalf of the Global Fund's Voluntary Pooled Procurement mechanism (VPP) and the Affordable Medicines Facility for Malaria (AMFm). In this type of role, CHAI will often defer to the organization on behalf of which it is negotiating to take the quality assurance and quality control measures CHAI would normally take.

In addition to CHAI's efforts to ensure the quality of the products purchased, procurement agents, Ministries of Health and non-governmental organizations (NGOs) also bear significant responsibility in ensuring the quality of drugs. Procurement Agents are responsible for ensuring that the drugs are handled in a manner consistent with preserving their quality during transport from the manufacturer to a port of entry into a country. Procurement Agents may also be responsible for conducting pre-shipment inspections to ensure the quality of the products and integrity of the shipment and/or conducting quality control testing before, during, or after transport to the port of entry to verify that the drug quality has in fact been preserved. Similarly, Ministries of Health, NGOs or other organizations involved in distributing drugs *within* a country are responsible for ensuring that the drugs are handled in a manner consistent with preserving their quality during this distribution process. These organizations and/or the laboratories associated with them should conduct in-country quality control testing to verify that drugs have in fact been handled appropriately and that drug quality has not been impacted since arrival into the country. These responsibilities are further discussed in the "Country and procurement agent responsibilities" section.

[1] Various technical terms are used throughout this document. Annex 2 contains a glossary for key terms.

A. CHAI's quality policies in its role as a negotiator/facilitator of access to prices and other terms for drugs

When CHAI negotiates agreements with pharmaceutical companies on behalf of CHAI's Procurement Consortium of developing countries, it is acting as a negotiator and facilitator of access to attractive prices and other terms for drugs. The prices CHAI negotiates are often referred to as ceiling prices and are available to all countries that are members of CHAI's Procurement Consortium. In this role, CHAI undertakes a set of quality assurance measures to ensure product quality and patient safety. These include:

1. Ensuring that suppliers have completed human bioequivalence studies or the appropriate clinical studies for the product(s) in question;
2. Verifying that suppliers have submitted a dossier to a stringent regulatory authority (SRA).[2] This verification should be in the form of confirmation from the SRA;[3] and
3. Confirming the manufacturer's production facility operates under current Good Manufacturing Practice (cGMP)[4].

CHAI facilitates procurement of products that have either been approved by a SRA or that have been submitted to a SRA for regulatory approval.

B. CHAI's quality policies in its role as purchaser

CHAI acts as a purchaser through its UNITAID-funded Pediatrics and Second-Line HIV/AIDS Treatment Project. Though rare, CHAI may also purchase drugs in an emergency situation to address an imminent stock-out in a CHAI Procurement Consortium country.

CHAI pursues the following quality assurance measures in its role as purchaser:

1. All of those listed above in section A;
2. Conducting independent evaluations of product dossiers (including bioequivalence data in the case of generic products) for any products currently under review by a SRA;

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[2] A SRA is defined as a regulatory authority which is (a) a member of the International Conference on Harmonisation (ICH); or (b) an ICH Observer (as specified on www.ich.org). As of the date of this policy, ICH observers currently include the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and World Health Organization (WHO).

[3] Submission of a product dossier for regulatory approval ensures that there is a robust body of data in place for the product including, but not limited to, human bioequivalence data, stability studies, and dissolution tests. It also ensures that the Active Pharmaceutical Ingredient (API) and Finished Dose Formulation (FDF) are manufactured in a facility under cGMP.

[4] Valid cGMP authorities include SRAs and regulatory authorities participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S). For PIC/S, please refer to www.picscheme.org.

3. Requiring and reviewing audit reports from SRAs, with the right to conduct periodic independent quality audit(s);
4. Requiring and reviewing that there is sufficient stability data in accordance with CHAI's stability policy (which is attached as an annex to this document);
5. In some occasions, conducting pre-shipment inspections to ensure the quality of the products and integrity of the shipment;
6. Requiring that suppliers' provision of products meet the specifications submitted in regulatory dossiers, including but not limited to use of approved API sources and manufacture at a cGMP compliant facility;
7. Requiring suppliers to ensure that the product complies with country level drug regulations and quality standards;
8. If the country actively registers medicines, requiring that suppliers have registered the product in the country of destination, or obtained a waiver for such a registration; and
9. Unless justified otherwise, requiring regular and independent laboratory testing of randomly selected batches as detailed below. Laboratory tests performed include: appearance, identity, assay, related substances, content uniformity, and dissolution.

Dossier assessments

CHAI will accept the recommendation of the Global Fund Expert Review Panel (ERP), or an equivalent body. The ERP review is intended to identify if the product is deemed to be at high-risk for not receiving stringent regulatory approval. ERP recommendations are binding.

For products that have been submitted for regulatory approval and that are undergoing regulatory review, CHAI requires suppliers to provide a copy of the entire product dossier that has been submitted to the regulatory authorities. Through a qualified third party, CHAI conducts detailed dossier assessments of the information that has been submitted for approval to ensure its completeness. The Chemistry, Manufacturing and Controls (CMC) as well as bio-equivalence sections of the dossiers are reviewed, gaps in the package are identified, and the criticalities of the information gaps are assessed. If after review of the dossier, the product is deemed to be at high-risk of not receiving stringent regulatory approval, CHAI may choose not to procure the product.

Quality audits / inspections

Manufacturers are required to provide copies of reports from audits conducted on the factories in which the drugs are produced, for the past two years, as follows:

- Copies of audit reports by the World Health Organization's Prequalification Programme (WHO), U.S. Food and Drug Administration (FDA) or other SRA if these agencies have

audited the Active Pharmaceutical Ingredient (API) and Finished Dose Formulation (FDF) manufacturing facilities in the past two years ; or

- Copies of all audit reports conducted by regulators that are members of the Pharmaceutical Inspection Cooperation Scheme (PIC/S) for the API and FDF manufacturing facilities, if the WHO, FDA, or other SRA have not audited the facility in the past two years.

Although existing audits may be sufficient, CHAI reserves the right to conduct an on-site audit. CHAI will generally use third parties consultants to conduct these audits.

Examples of situations in which CHAI may elect to conduct an audit include, but are not limited to, the following: after a PIC/S agency identifies problems in the facility, and/or if a limited number of PIC/S audits have occurred in the past 2 years.

Audits conducted by CHAI or its agents will serve as an ongoing check of the quality of the facilities in which the products are manufactured. The scope of these audits may extend beyond GMP assessments to purchase records as well as the source of APIs.

Quality control

Regulatory approval and QA procedures confirm that a product is produced according to quality standards, but do not ensure against deviations that may arise during the production of a particular batch of drugs. Quality control testing serves as a check against such deviations. When acting as a buyer, CHAI follows established QC procedures to ensure that specific batches conform to the necessary quality standards. Testing of samples collected prior to the transport of the product to the destination country is done by a testing agent (TA) chosen by CHAI. QC testing prior to transport can only verify that a batch has been manufactured appropriately, not that it has been properly transported and stored while in transit to the destination country. Therefore, CHAI's QC activities should be supplemented with further QC measures in country. Countries have the responsibility of establishing QC measures to ensure continued product quality during distribution, and to prevent counterfeiting.

All products that are procured for CHAI treatment programs are subject to random quality testing. Products that are not yet approved by a SRA are subject to 100% batch testing, i.e., the TA will sample all batches for analytical testing in the laboratory. Procured products that are approved by regulatory authorities are subject to a minimum of 20% batch testing, i.e., the TA will randomly sample 20% of procured batches for QC testing. CHAI reserves the right to test every batch.

Pharmacopoeial Monographs and Test Methods

Pharmacopoeial Monographs are established reference documents containing specifications and test methods. These monographs provide an independently verified method and, ideally, detect aberrations in the synthetic process. Testing will be performed against such monographs, when available. An Acceptable Monograph is one that has been published in the US Pharmacopoeia or International Pharmacopoeia or has been published to the web sites of the US Pharmacopoeia (www.usp.org) or International Pharmacopoeia (www.who.int). Testing against monographs published in other pharmacopoeia may be permitted by CHAI.

In the absence of a published monograph, testing may be based on published methods, methods developed by the TA, or methods developed by the supplier. In the case of methods developed by the supplier, the supplier must validate the method according to International Conference on Harmonisation (ICH) guidelines, and the supplier is responsible for providing a validation report to the TA. Further, the supplier is expected to support method transfer by providing relevant samples and necessary technical assistance to the TA.

If a method is subsequently published by the US Pharmacopoeia or the International Pharmacopoeia, the TA will change its testing methods to use the pharmacopoeial method within 120 days. CHAI will be responsible for final decisions regarding selection of test methods, and will provide documentation of this decision to the supplier.

Samples and Working Standards

Suppliers are required to provide, upon request, the following for every Batch (in case of Laboratory testing) and for every Shipment (in case of Pre-shipment Inspection), in order to enable proper testing:

(i) Samples for Laboratory Testing in quantities specified by TA
(ii) Samples for Pre-shipment Inspection
(iii) Placeboes sufficient to test one batch

The TA is responsible for maintaining reference materials required to perform testing. Primary standards may be obtained from pharmacopoeial organizations and used to establish working standards. Materials for working standards may be requested from suppliers and may be used for multiple batches. Crude samples of API with characterized levels of critical impurities may be used to quantify impurity levels in place of primary standards of these impurities. Such samples may be obtained from the supplier and may be used for multiple batches.

Retain Samples

The supplier must collect and maintain retain samples of FDF and API for every batch produced according to a Standard Operating Procedure (SOP) addressing retain samples. The supplier is

required to provide a copy of this SOP to CHAI. The size of these retained samples should be large enough so that a sample can be provided to CHAI, upon request.

Certificates of Analysis

The supplier is responsible for supplying Certificates of Analysis and packing lists of every batch supplied.

Pre-shipment Inspections

When a pre-shipment inspection has been conducted, suppliers shall not ship the inspected stocks unless a First Inspection Report is received from the TA. CHAI reserves the right to inspect every shipment.

Stability policy

Products procured must comply with CHAI's stability policy, which is attached as an annex to this document.

Product Recall

Should CHAI or the TA notify suppliers of a quality concern with their product, suppliers are expected to respond quickly and to work with CHAI and the TA to determine if the concern is valid.

Suppliers are responsible for communicating, conducting, and paying for any product recalls that may be required. Suppliers are required to provide a copy of the SOP to be followed in case of a product recall.

Suppliers are obligated to notify CHAI of any voluntary recall and of any warning letter received from a SRA.

C. Exceptions to quality assurance standards described above

CHAI believes that all medicines should be subject to the same QA/QC standards and supports efforts to move in that direction. However, in exceptional circumstances, CHAI will facilitate procurement of medicines that have not yet been submitted for regulatory approval to a SRA, but which are manufactured at a cGMP compliant facility. For example, exceptions to the requirement

of a SRA-submitted dossier must be made for drugs for opportunistic infections (OIs) since there is a limited availability of quality-assured OI drugs that are registered in CHAI program countries. In addition, CHAI makes best efforts to only procure products where the API and the FDF are produced in cGMP facilities. In exceptional and time-limited events, CHAI may choose to procure a product that does not meet this requirement to fulfill a serious medical need when no other option is available. Decisions to do so will be jointly made by CHAI's Clinical and Drug Access team

Manufacturers of drugs that have not submitted a dossier to a SRA are required to complete the Interagency Pharmaceutical Product Questionnaire and, except under exceptional circumstances as described in the prior paragraph, must manufacture the FDF in a facility under cGMP.

D. Country and procurement agent responsibilities

Procurement agents must ensure that the responsible parties store the product properly until transport and that the responsible parties transport the product under appropriate conditions.

For all medicines, regardless of the purchasing or procurement agent, countries play a critical role in ensuring that drug quality is preserved until it reaches the patient. This role includes the following actions:

- Properly storing, transporting, and distributing drugs to retain their integrity;
- Clearly stipulating quality standards for both API and FDF in all tenders and contracts;
- Establishing and following rigorous in-country quality control procedures for all incoming shipments of pharmaceuticals to ensure that drug quality has not been impacted during the in-country transportation and distribution process;

Failure to implement and execute the above measures can lead to several risks:

- Improper storage conditions can cause degradation of the drug (e.g., delamination of the pill) to the point where the product would need to be removed from the market.
- Incomplete QC measures in country can unnecessarily burden countries with problems that occurred prior to the product's arrival in country.

Annex 1: Stability Policy

CHAI Stability/Shelf-life Policy

CHAI's goals as an "Honest Intermediary" are to (a) fairly represent all parties for sourcing essential medicines, (b) negotiate the lowest possible prices for Quality medicines that allow for sustainable supply and (c) ensure patient safety and efficacy. These goals inform CHAI's policy, outlined below, regarding Stability testing and assignment of a Shelf-life for products procured through CHAI's services.

All products procured by CHAI are assigned a shelf-life, expiry date or some other indicator (e.g., retest date) of the date by which the product must be used or else re-certified for use. In cases where a shelf-life has been established through agreement of the Manufacturer and a Stringent Regulatory Authority (SRA) CHAI will defer to this agreement. In exceptional cases where a shelf life has not been established, CHAI may make an estimate based on an assessment of results of on-going stability testing and guidance published by the International Conference on Harmonisation (ICH)

The supplier is expected to provide justification for claimed shelf-life and expiry dates to CHAI. If the justification and ongoing stability studies meet CHAI's approval, written documentation of this will be provided to the supplier. Any shelf-life subsequently granted by a SRA will be accepted by CHAI.

Determining shelf-life

The longest possible shelf-life, typically two years at a minimum, is desired in order to simplify procurement.

Shelf-life is generally assigned based on stability data from real-time studies. ICH guidelines allow but do not guarantee the extension of shelf-life beyond real-time data based on accelerated stability data, with the maximum extension being two times (2x) the duration of the accelerated stability up to a maximum of 12 months. Such an extension will be evaluated on a case-by-case basis. CHAI will require that accelerated studies be performed at 40°C/75% relative humidity (RH) rather than 30°C/65% RH. It is strongly encouraged for products sold into zone IV countries that real time stability tests be performed at 30°C/65% RH. The supplier must commit to continuing both accelerated and ambient stability tests and providing updated information to CHAI every three months.

In the case that a supplier lacks sufficient data to support two year shelf-life, justification for shelf-life beyond real time data may also be supported by long-term stability information generated on pilot batches, provided that such batches are determined to be representative of the actual

manufacturing process output. This information would typically provide the desired 1 year accelerated period to justify a two year shelf-life. The supplier is responsible for providing this data. Failure to do so may result in a delay to allow time for sufficient collection of stability data.

To justify continued use beyond the shelf-life supported by real-time data, accelerated stability results should provide clear evidence that degradation has not occurred. However, monitoring the appearance of chemical degradants in stability testing is insufficient to justify extension of shelf-life. Drug product quality issues such as dissolution and physical appearance also need to be determined. There should be proof that test methods are stability indicating. Results from ICH stress that testing may also be used to determine the degradants likely to arise in long-term storage. CHAI may apply thermokinetic evaluation to justify extension of shelf-life beyond existing data. Results submitted by suppliers to justify longer shelf-life may be evaluated by outside consultants employed by CHAI.

Failures of stability testing may result in a product recall. As the procurement agent for such products, CHAI must be promptly and fully informed of such circumstances. The supplier is responsible for the swift notification of all customers that such circumstances have occurred, and all measures must be taken to ensure that a rapid recall of products whose stability may be compromised does occur. The supplier must have an SOP in place for dealing with such failures.

Procurement implications

For some products, such as those that have not yet been approved by an SRA, actual stability data to support the claimed shelf-life may not be available. CHAI may decide on a case-by-case basis to procure such products prior to the availability of such supporting data. This decision will be based on a special need for a product that conveys a clear advantage to alternatives. The rationale used in reaching this decision will be documented along with existing stability data.

CHAI will inform purchasing organizations/governments of the potential risk of products secured by CHAI that lack sufficient data to support claimed shelf-life.

CHAI will provide updates, gathered from the ongoing stability studies being performed by suppliers, on this risk and will notify purchasers of any concerns that arise in testing.

Annex 2 – Glossary

API – Active Pharmaceutical Ingredient – The drug portion of a pill, also referred to as drug substance.

Batch – A batch is a defined quantity of pharmaceutical product produced in a single process or series of processes so that it is expected to be homogenous. The batch should be identified by a unique combination of letters and numbers so that the individual product can be traced to production records and a certificate of analysis. Each package should be labeled with the batch number.

Bioavailability – Rate or extent that the API is absorbed from the drug product to be available at its site of action. Peak and cumulative levels of the API in the blood are typically reported

Bioequivalence – Demonstration that two drug products have comparable bioavailability. Typically these studies are performed by a generic company comparing their product to the originator or designated comparator product. Establishment of bioequivalence allows the generic company to seek marketing approval based on clinical data generated by the comparator product.

Certificate of Analysis (COA) – A document showing the results of analytical testing for a particular batch along with specifications the product must meet. This document should be signed by the analyst(s) who performed the testing and a reviewer.

CMC – Chemical Manufacturing Control – Detailed description of manufacturing process for either API or drug product. This will include quality requirements for raw materials, intermediates and product as well as full characterization of the product.

Dossier - Package of information to be filed with a regulatory authority to support registration of a drug product. This will include complete biological data (bioequivalence, clinical results, toxicity testing), manufacturing data (CMC) and stability testing results.

Excipients – inactive components of a drug product that may affect dissolution, stability, integrity, color, bioequivalence

Finished Dose Formulation (FDF) – Drug product that contains API and excipients.

Finished Pharmaceutical Product (FPP) – Drug product that contains API and excipients along with packaging and labeling.

Generic Product – Version of a drug product produced by company other than the originator. Such products must meet all the same quality requirements as that of the originator and demonstrate bioequivalence.

Good Manufacturing Practice (GMP or cGMP) – Standard practices to be followed by manufacturers of drug products, drug substances, etc. with the intent of maintaining consistent

product quality. This includes clearly traceable documentation of instructions, results and materials used which ensures that deviations that may lead to a change in product quality do not occur. The lower case c denotes use of current standards for GMP, which may evolve.

Innovator (or Originator) Pharmaceutical Company – The company filing first registration of a drug product including clinical data. This company may or may not be the inventor.

Interagency Pharmaceutical Product Questionnaire – Standardized document to be completed by potential manufacturer for evaluation of the FPP. It details product information, manufacturer information, regulatory information, product specification and analysis, stability, labeling, therapeutic equivalence and source of API. By standardizing format and content it is hoped that supplied information will be more complete.

Laboratory Tests

Identity – The intent of this test is to verify that the API in the drug product is correct. High performance liquid chromatography (HPLC) is more common that spectroscopic methods due to the need for increased specificity.

Purity or related substances – Normally performed by HPLC, the goal of is to detect degradation or contaminants arising in the formulation process.

Assay – Assay serves as both a check on purity results and as a determination that the drug product contains the prescribed amount of active ingredient. Again, HPLC is the method of choice.

Content Uniformity – An effort to verify that units of the drug product are uniform. This can be difficult for drugs with low levels of API and should be considered as a rough check.

Dissolution test – This test is intended to verify that drug product will dissolve as expected. Contrary to expectations such tests are not designed to mimic dissolution in patients but rather to detect variations in the formulation process. Consistency in the formulation process is tied to performance during clinical trials. The dissolution test is thus an indirect predictor of efficacy. This leads to the use various dissolution media and difficult interpretation of results. Failures in the dissolution test may arise during storage that may or may not result in the loss of efficacy; failures should be taken seriously as they are indicative of a physical change in the drug product.

Physical Appearance – A broad description of the appearance of either a drub substance or drug product. For a drub substance this typically includes color and crystallinity. Drug product descriptors include color and that tablets are not broken.

Preshipment Inspection – An inspection of product scheduled for shipment that includes evaluation of correct labeling, quantity and shipping information. This inspection may also include sampling of product for QC testing.

Quality Assurance (QA) – The overarching set of regulations intended to ensure that a drug substance or drug product is manufactured according to defined procedures. The philosophy is that drug product made consistently via the same process used to generate clinical data will elicit the same biological results. Allowing no changes in the process should ensure consistent quality, safety and performance of drug products.

Quality Audits – On-site inspections of manufacturer facilities with the goal of ensuring that cGMP is followed. This effort will include inspection of the physical plant, records, personnel qualifications and training, raw material and product handling. Such audits are performed by a variety of regulatory agencies, purchasing agents, independent contract auditors and customers.

Quality Control (QC) – Despite adherence to cGMP and QA practices it may still be possible for an API or a drug product to be substandard or contaminated through unforeseen factors. Chemical and physical tests are performed on products to verify that they meet quality standards.

Reference Standards (primary, working) – Some product testing requires comparison to material of established quality, i.e., reference standards. Primary reference standards typically are high purity with well-defined quality. These may be costly and available in limited quantities. Readily available material of high quality may be used as secondary or working standards providing their quality is established against a primary standard.

Retain Samples – Samples of a drug product or API that are taken and stored by a manufacturer or distributor. The intent of taking such samples is to assist in identification of the source of any problems with the product observed further in the distribution chain. SRAs approving drug products oblige suppliers to keep retain samples.

Stringent Regulatory Authority (SRA) – Regulatory agency from a country deemed stringent enough that their findings are acceptable to the Global Fund and other agencies. These countries are defined as members of the International Committee on Harmonisation (European Union member States, the U.S. and Japan), ICH Observers (Switzerland, Canada) and ICH Associates (Australia, Norway, Iceland & Liechenstein).

Thermokinetic Evaluation – The extension of shelf-life from stability data may be justified by evaluation of degradation with respect to temperature, assuming zero order kinetics. In practice, if little or no decomposition has been observed a longer term stability may be confidently predicted.