Post-approval Changes in Analytical Testing Laboratory Sites - PAC-ALTS

GUIDANCE FOR INDUSTRY

INTRODUCTION

This approved guidance (April 1998) provides recommendations to pharmaceutical sponsors of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to change an analytical testing laboratory site for:

- drug product containers, closures,
- packaging materials
- in-process material testing
- drug product testing during the postapproval period.

Analytical testing laboratories include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials as well as those performing stability testing.

When Changing Testing Laboratories
FOUR key conditions for a CBE Supplement need to be met

Changes in an approved application to allow for the use of a different facility or establishment, including a different contract laboratory, normally require FDA approval before the change is made (21 CFR 314.70(b)). FDA regulations at 21 CFR 314.70(a) provide that applicants may make changes to an approved application in accordance with a guidance, notice, or regulation published in the Federal Register that provides for a less burdensome notification of the change (e.g., by notification at the time a supplement is submitted or in the next annual report).

This document provides guidance on a less burdensome approach to providing notice (i.e., Changes Being Effected (CBE) supplement) of certain post-approval changes within the meaning of 314.70(a).

This guidance does not comment on or otherwise affect compliance/inspection documentation that has been defined by CDER's Office of Compliance or FDA's Office of Regulatory Affairs.

This guidance does not affect any post-approval changes other than the ones specified. For changes filed in a Changes Being Effected (CBE) supplement (21 CFR 314.70(c)), the FDA may, after a review of the
supplemental information, decide that the changes are not approvable.

FOUR KEY CONDITIONS
- Meets 21CFR 314.70(d)
- Meets PA Commitments
- Adequate Facilities
- TWO Years cGMP

DISCUSSION
An analytical testing laboratory site change can be submitted as a Changes Being Effectected (CBE) supplement if:

1. The test method(s) approved in the application or methods that have been implemented under 21 CFR 314.70(d) are used,
2. All postapproval commitments made by the applicant relating to the test method(s) have been fulfilled (e.g., providing methods validation, samples),
3. The new testing facility has the capability to perform the intended testing, and
4. The new testing facility has had a satisfactory current good manufacturing practice (cGMP) inspection within the past 2 years.

Prior to submitting analytical testing laboratory site change supplements, an applicant should determine that the laboratory has the capability to perform the intended testing. Information to support the capability of a laboratory to perform the intended testing (e.g., comparative data, cGMP history of performing the test, appropriate standard operating principles (SOPs), equipment and personnel in place) should be available for FDA investigator review.

Data demonstrating that the new testing facility can perform the analytical test(s) being transferred need not be included in the supplement, except for biological tests. In the case of biological tests, comparative data from an approved analytical testing laboratory site and the new testing facility should be included in the supplement with the exception that this information need not be submitted for the pyrogen and bacterial endotoxin tests (LAL Test).

Information about the cGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP reports information on the cGMP compliance status of firms which manufacture, package, assemble, repack, relabel or test human drugs, devices, biologics and veterinary drugs.

FOI HANDBOOK
All FOI requests must be in writing and should follow the instructions found in the reference entitled:
A Handbook for Requesting Information and Records from FDA.
An electronic version of this reference handbook is available on the Internet at http://www.fda.gov/opacom/backgrounders/foiahand.html

When submitting a supplement for a change in an analytical testing laboratory site, the applicant should confirm in a written statement why a PAC-ATLS CBE supplement is appropriate (i.e., the four circumstances listed above exist).

The supplement should also contain the name and address of the new analytical testing laboratory site and a full description of the testing to be performed by the new facility.

The supplement should be clearly identified in the heading and text as being filed under PAC-ATLS. If the proposed change in the analytical testing laboratory site does not fall within the scope of PAC-ATLS, it is recommended that the change be filed in a prior approval supplement.
GLOSSARY OF TERMS
The following terms are being provided to assist the reader in using this guidance document.

Active Ingredient:
This term is used interchangeably with active pharmaceutical ingredient (API) and drug substance.
Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient.
The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3(b)).

Biological Tests:
Biological tests include animal, cell culture or biochemical based testing that measures a biological, biochemical or physiological response.

Component:
Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

Drug Product:
A finished dosage form, for example, tablet, capsule or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4)).

Inactive Ingredients:
Any component other than an active ingredient (21 CFR 210.3(b)(8)).

In-process Material:
Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)).

Satisfactory Current Good Manufacturing Practice (cGMP) Inspection:
A satisfactory cGMP inspection is one during which:-
(1) no objectionable conditions or practices were found during an inspection (No Action Indicated (NAI)) or,
(2) objectionable conditions were found, but corrective action is left to the firm to take voluntarily and the objectionable conditions do not justify further administrative or regulatory actions (Voluntary Action Indicated (VAI)).

ALT-SUMMARY
- Applies to all analytical tests at any stage of drug product's life-cycle.
- Lab must prove test can be fully performed with accuracy and precision.
- Lab must prove its testing capability
- Lab must have a history of performing the specific test (i.e. written data.)
- Lab must have appropriate SOPs for the test(s) concerned.
- Lab must have suitable calibrated equipment for the test(s).
- Lab must have trained personnel for the test(s) (written training records).
- Lab’s overall capabilities must be available for agency inspection.
- Lab’s GAP must be satisfactory (Request Firm’s GAP Report from FDA’s Freedom of Information (FOI) Office.)
- Update FDA-OGD via the Annual Report or a future Supplement (whichever is sooner.)
PAC-ATLS GUIDELINE - POSTAPPROVAL CHANGES
Analytical Testing Laboratory Sites

‘...the laboratory must not only say that the tests can be performed but prove that they can be done...’

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<tbody>
<tr>
<td>1.</td>
<td>This change procedure applies to approved drug products only.</td>
<td>Yes</td>
<td>No</td>
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<td>2.</td>
<td>Applies to all analytical tests at any stage of drug product's life-cycle - from raw material analysis to post approval stability.</td>
<td>Yes</td>
<td>No</td>
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<td>3.</td>
<td>A copy of the laboratory's Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office.</td>
<td>Yes</td>
<td>No</td>
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<td>4.</td>
<td>The chosen laboratory passed a satisfactory cGMP inspection within the last two years.</td>
<td>Yes</td>
<td>No</td>
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<td>5.</td>
<td>No objectionable conditions or practices were found during the last inspection.</td>
<td>Yes</td>
<td>No</td>
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<td>6.</td>
<td>Where objectionable conditions were found, adequate corrective action has been taken to satisfy the FDA's initial objections.</td>
<td>Yes</td>
<td>No</td>
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<td>7.</td>
<td>Analytical testing Laboratory (ATL) must prove test can be fully performed with accuracy and precision.</td>
<td>Yes</td>
<td>No</td>
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<td>8.</td>
<td>ATL must prove its testing capability for each and every test.</td>
<td>Yes</td>
<td>No</td>
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<td>9.</td>
<td>ATL must have a recorded history of performing the specific test(s) (i.e. a written track record.)</td>
<td>Yes</td>
<td>No</td>
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<td>10.</td>
<td>ATL must have appropriate SOPs for the specific test(s) and procedures.</td>
<td>Yes</td>
<td>No</td>
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<td>11.</td>
<td>ATL must have suitable calibrated equipment for the test procedures</td>
<td>Yes</td>
<td>No</td>
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<td>12.</td>
<td>ATL must have suitable information to support its capability to perform the intended analytical testing procedures.</td>
<td>Yes</td>
<td>No</td>
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<td>13.</td>
<td>ATL must have trained personnel to perform the test procedures (availability of updated training records, specific to the required analysis)</td>
<td>Yes</td>
<td>No</td>
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<td>14.</td>
<td>ATL overall capabilities must be available for agency inspection.</td>
<td>Yes</td>
<td>No</td>
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<td>15.</td>
<td>FDA will be informed of the change being effected, via the Annual Report or a future Supplement (whichever is submitted sooner.)</td>
<td>Yes</td>
<td>No</td>
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<td>16.</td>
<td>Where a supplement is filed, it is clearly identified in the heading and text as being filed under PAC-ATLS rules - and,</td>
<td>Yes</td>
<td>No</td>
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<td>17.</td>
<td>A written statement is included why a PAC-ATLS CBE supplement is appropriate (i.e., the four circumstances listed above, all exist.)</td>
<td>Yes</td>
<td>No</td>
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