Impact of API (Active Pharmaceutical Ingredient) Source Selection on Generic Drug Products

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Abstract

The pharmaceutical industry is emerging as a significant industrial sector with tremendous potential for providing innovative drugs to treat life-threatening diseases as well as for providing economical generic alternatives of supreme quality. Hence this sector is not only responsible to provide the much desired boost to the health of the society, especially of the developing countries, but also it is a competitive yet profitable sector from a business perspective. Currently, the primary focus of the pharmaceutical industry is to raise the bar for the quality, safety and efficacy of the drug products that are made available in the global market place. Product quality, price of raw materials [API (active pharmaceutical ingredient) and excipients] and market return competition are vital factors that determine the longevity or existence and profitability of a company in the crowded pharmaceutical market. Hence these critical factors receive special consideration from drug product manufacturers. Active Pharmaceutical Ingredient (API) is the primary constituent of a pharmaceutical drug product that governs the final cost of the drug product as well as the commercial profit earned by the company. Most of the major generic drug manufacturing companies have their own API manufacturing facility and hence may not prefer to screen independent API suppliers as part of their generic drug development plan to procure additional API. Contradiuctory, the generic drug manufacturers who do not synthesize the API themselves are dependent on external and independent API manufacturers for procurement of the API. Such generic drug manufacturing companies have to select suitable API suppliers by adapting a risk averse approach. This article presents an informed and comprehensive discussion on the primary and alternate API supplier selection processes for generic drug products manufacturing firms. This API supplier selection process can be categorized into several stages which include preliminary assessment, documents review, samples analysis, onsite or offsite audit, results evaluation and final approval or rejection. This API selection process includes the anticipated product specific risk assessment with relation to API characteristics, specifications, analytical results, document review observations and inspection results. A generic drug product manufacturing company can choose an alternative API supplier or change the existing API supplier either during the development phase or after development of the drug product. Generic drug product manufacturing companies should rework on development activities if any API supplier change happens during the development phase. API supplier change or addition of an alternative API supplier has to be followed as per SUPAC guidance for US market and VARIATION filing procedures for European market.

Keywords: API supplier selection; Pharmaceutical industry; Generic drug product; Risk assessment; Price competition; SUPAC; API supplier change and variation filing

Introduction

Drug products are formulated with API and excipients. Drug product has to enter the market in any country by adapting either of the two processes viz. new drug product approval process or generic drug product approval process. Generic drug products are similar to the new drug products in safety, efficacy and quality. USP [1] has published the manual for API supplier selection "USP pharmaceutical ingredient supplier qualification program". Generic drug product approval process was introduced with the intent of marketing the drug products at a lower cost than the innovative drug product so as to provide monetary benefit to the patients. Since, all the approved generic drug products are similar to the innovative drug product; cost of the generic drug product plays a critical role in helping the generic drug product manufacturer acquire a significant market share in the competitive and crowded generic pharmaceutical market. The major share of the generic drug product price is mainly driven by cost of the API. Also, API attributes such as material purity, physical and chemical properties are the discriminating factors that decide the generic drug product quality. So the generic drug manufacturers are enforced to select the suitable API material with required attributes and an appropriate API supplier for the drug product development [2-4]. The decision to choose an API supplier is an important decision in generic drug product development since most of the generic companies do not have their own API development and manufacturing unit. In the highly competitive generic business it is important for the drug product manufacturers to maintain an entrusted long term strategic relationship with the API suppliers to get an early access to high quality active pharmaceutical ingredients as well as to overcome the pricing burdens.

Generic drug product manufacturers have to overcome numerous obstacles with respect to API suppliers whilst selecting the most suitable API supplier. In recent years all the regulatory bodies across the globe have become stringent with adherence to quality standards as well as adherence to cGMP standards are concerned. Additionally, the...
API manufacturers frequently update the CMC section as part of the
cost improvement programmes.

In addition to the ICH (international conference on harmonization)
Q7 guidance, most API manufacturers have comprehensive knowledge
of GMP principles. Most API manufacturing facilities have traditionally
had good quality systems, change-controls systems and good laboratory
controls. Dissimilarly, in recent years, some GMP inspections have
also revealed that some API manufacturers still continue to struggle
to achieve sustainable GMP compliance. Most generic drug product
manufacturers have failed GMP inspections due to lack of laboratory
controls; quality system; equipments; records and reports. Below
(Table 1) has represented the most common GMP inspection finding
in recent years.

API Supplier Selection Factors

Generally, the quality attributes of the API are classified into
three classes, namely, Administrative, Formulation and Analytical.
Quality of an API can be determined by performing physical as well
as chemical evaluation. Every analytical test procedure undertaken
to evaluate the quality attributes of an API has to be developed and
validated according to the ICH and national regulatory requirements.
Each quality attribute class of the API has been discussed below.

Administrative related

Administrative attributes are API GMP facility, quality management
system, manufacturing practices, manufacture and deliverable
capacity, documentation practices and price. All the administrative
related attributes can be evaluated at the API supplier selection phase.
Also it is beneficial to check the GMP status of the API supplier with
respect to the targeted countries. The supplier/manufacturer should
provide all the required regulatory documentation such as open part
DMF (drug master file), analytical validation documents and other
regulatory documents (TSE free, GMO free etc.). DMF/CEP (certificate
of suitability) online status should be confirmed.

Synthesis related

API supplier selection team should consider API synthetic
route including starting material, impurities, residual solvents,
polymorphism, isomerism and manufacturing process. API synthetic
route will impact all variables such as impurities, residual solvents
and physicochemical properties of API. Synthetic route can have
number of branches. Each branch of starting materials should be
evaluated and characterized as per GMP guidance. Manufacturing
steps should have appropriate control strategy for impurities, residual
solvents and maintain the quality of final API. Starting material
should be incorporated as a significant structural fragment into the
structure of final API. An applicant generally may not justify the use
of a commercially available chemical as a starting material. Applicants
should identify all proposed starting materials or source materials and
provide appropriate control to these starting materials to detect possible
impurities in the starting material. Regulatory agencies will assess
whether the controls implemented on API and API manufacturing
process are adequate or not for the control of impurities [5-7].

Formulation related

Formulation attributes are solubility, particle size, bulk density,
polymorphism and Flowability. As part of QbD (quality by design)
approach, all these attributes should be studied in the drug product
development phase. All the quality variables of the API material are
discussed in the below section [8-10].

Analytical related

The analytical attribute of primary importance is the specification
of the API. If the API is listed in the Pharmacopoeia, then the
manufacturer should manufacture API that complies with the current
version of the pharmacopoeia specification. If the API is not described
in any pharmacopoeia, then the specification should follow the
standards described in the general pharmacopoeia monograph, ICH
Q6A guideline and country relevant regulatory guidelines. Some of the
key specification parameters are described below [11-13].

Identification: Identification of the API can be performed either
by chemical analysis or by instrumental analysis. Most of the API
monographs recommend performing two specific identification
tests e.g. IR or HPLC. The results of these tests should be taken into
consideration for the selection of an API supplier.

Water content: Water content is evaluated mainly by two methods
such as water content by Karl Fischer titration and loss on drying
(LOD). LOD test is kind of limit test for water content in the API
material. Water content can show high impact on the drug product
quality (hardness, dissolution, friability, impurity profile etc.) and
manufacturing process. API supplier selection team should consider
the theoretical value and specification value [14,15].

Particle size distribution (PSD): API material PSD is a significant
attribute which could alter the drug product quality attributes like
dissolution, Flowability, blend uniformity, etc. and could even
define the bioavailability for certain drugs. Hence, the particle size
specification shall be decided at the development phase; the target
specifications shall be established and harmonized. Decision tree #3
of ICH Q6A guideline has explained implementation of particle size
testing [16].

Polymorphism: API polymorphic characteristics have significant
importance in the generic drug products as polymorphism could
significantly influence the drug solubility, bio equivalence and stability.
Generic drug product manufacturers may be compelled to use certain
specific polymorphic forms of the API to circumvent the patents and
associated legal issues. Polymorphic form of the API may change
due to changes in the thermal or stress conditions, hydrolysis or by
forming co-crystals with other excipients. The synthetic route selected
for the manufacture of the API could influence the polymorphic form
stability. Hence the drug product manufacturers have to perform
thorough evaluation of the various polymorphic forms of the API
before confirming the appropriate and active polymorphic form of the
API. It is recommended to the generic drug product manufacturers to
evaluate the solid state stability at 40°C/75%RH and 50°C conditions
(other conditions may be applicable on a case by case basis) by DSC,
XRD, TGA analysis. Stability studies conducted on drug product
development batches may provide information on the polymorphic
conversion of several API isomers and consequently affect the selection
of the API vendor as well. Decision tree #4 of ICH Q6A guidelines was
explained to perform polymorphic test in API finished analysis [17-21].

Impurities: API synthetic route is the source for impurities such as
starting materials, by-products, intermediates, degradation products,
reagents, residual solvents, heavy metals, inorganic salts and other
materials. All impurities are analyzed by using suitable validated
analytical techniques and the limits of permissible impurities should
comply with the ICH limits. But preferably tighter limits than those
prescribed by ICH are recommended for impurities. Generally,
degradation impurities and the extent of degradation would be
examined and evaluated by the generic drug product manufacturers.
Recently the subclass of genotoxic impurities has been comprehensively
researched and evaluated by the pharmaceutical industry and the health authorities alike to understand the impact that these genotoxic impurities have in humans. Hence genotoxic impurities should be thoroughly evaluated and accordingly documented by the generic drug product manufacturers. Genotoxic impurities and metal impurities have recently received special attention from both, the health authorities and the industry. Hence generic drug product manufacturers should give exclusive consideration to these impurities [22-31].

**Assay:** Assay results should comply with the specifications. The supplier evaluation samples should be analyzed using high quality standard materials. Further, API open part DMF evaluation would also confirm the assay results during API stability studies [30,31].

**Residual solvents:** ICH guidance has classified the residual solvents into three classes. Class-1: Solvents to avoid; class-2: Solvents to be limited; and class-3: Solvents without low toxic potential. Class-1 solvents are not recommended for usage in the API synthesis due to their high toxicity to the patient. Generic drug product manufacturers should ideally adopt the ICH recommendation of avoiding Class 1 solvents during selection excipients and packaging material as well. Residual solvents can be determined by using gas chromatographic (GC) method and other techniques. Drug product manufacturers may use solvents for coating or granulation or other manufacturing steps. The solvents that are used also need to be analyzed in the final drug product. Residual solvents quantities assessment should be discussed in the generic drug application [32-35].

**Microbial limits:** Microbial tests should perform for all kind of API materials to ensure the API microbial contamination. API selection phase should consider this test item. Acceptance criteria for microbial limits should be based on source of raw material and method of manufacture [36-38].

**Enantiomer purity:** Most of the APIs display the physical property of isomerism. The type of isomers existing for a particular API along with the percentage quantity of each isomer in the racemic mixture can be evaluated with established analytical procedures. Specific isomers of a single API may treat selective therapeutic indications from both, the health authorities and the industry. Hence generic drug product manufacturers should give exclusive consideration to these impurities [22-31].

- **Salt content:** The active moiety of most APIs is unstable. Hence the active moiety has a tendency to react with an acid or an alkali to yield the corresponding salt or an ester. Thus the API supplier should perform the content determination test for salt or ester form of the API. These tests can be quantified by using chemical or instrumental methods (HPLC, GC, Ion chromatography, AAS (atomic absorption spectroscopy) etc.). Genetic drug product manufacturer should conduct this test during API and drug product analyses [48-51].

**Stability data:** API stability studies data should be evaluated in the open part the DMF document. Knowledge of the stability of the API throughout its re-test period will provide insights on API degradation impurities. All these API related attributes should be evaluated comprehensively. The technical departments that generally are involved for evaluating API suppliers and the related information are samples analysis department, DMF review department and facility inspection department.

**Core departments**

The core departments involved in the drug development process are formulation development, analytical development, quality assurance, regulatory affairs and intellectual property rights (IPR) team. The roles and responsibilities of these departments in the drug product development is presented below. All departments should consider the relevant DMF format and pharmacopoeial monographs. Below (Table 2) has represented the regulatory countries, DMF format and pharmacopoeia details.

**Analytical development**

Analytical development team participates in supplier samples’ analysis, document review and risk assessment. Analytical development team should analyze the supplier shipment samples (at least three batches). Supplier’s samples should be evaluated by using either DMF method or pharmacopoeial methods (USP-NF or Ph. Eur. or JP monographs).

**Formulation development**

Formulation development team shall perform the formulation feasibility studies between the suppliers as well as it can also contribute...
in technical review i.e. Samples analysis results, document review, patents related and final results risk assessment.

Regulatory affairs (RA)

RA team will participate in the entire process of API supplier selection. RA team will actively involve in document review, evaluation of results and risk assessment [52-54].

Quality assurance (QA)

QA team should mainly focus on patents’ concerns for drug substance synthesis, polymorphism or residual solvents, impurities profile, particle size etc.

Supply chain management (SCM) team

SCM team should be involved in the selection process by verifying the conclusions from the other core departments and finalize the suitable supplier. SCM team will work on purchasing and logistics activities (Table 3).

API Supplier Selection Process Modules

API supplier selection process is the initial step in generic drug product development. Selection processes for primary and alternative suppliers and addition or change of suppliers will be discussed in three modules. (Figure 1) represents the generic drug product life cycle and highlighting the key decisions made with respect to API supplier at respective stage for drug product development (Module-1 to 3).

Module-1: Project initiation phase
Module-2: Product development phase
Module-3: Post product development

Module-1: Project initiation phase

Generic drug product development life cycle begins with the selection of suppliers/vendors for API, excipients and packaging configuration. API selection process should involve a quality and risk based approach by considering the API synthetic route, starting material characteristics i.e. Physical (polymorphic nature, hygroscopicity, particle size, bulk density etc.) and chemical properties (impurities profile, thermal behavior and residual solvents etc.). Generic drug product manufacturer will select the API supplier by executing the following steps,

1. Preliminary assessment
2. Document review
3. Samples analysis (minimum three batches)
4. Onsite or off-site audit
5. Results evaluation
6. API Supplier approval/rejection

Preliminary assessment: Literature review helps to better understand the ideal API characteristics and drug product development requirements before initiating the API supplier selection process. Based on the nature of the API and the drug product requirements; generic drug product manufacturer should assess the initial risk on each quality attributes. Presented below are few examples on evaluation of certain active pharmaceutical ingredients; as a case study performed for proposing the API risk assessment process. For example, Losartan Potassium has relatively high sensitivity towards polymorphic form conversion; Rosuvastatin and Atorvastatin are prone for oxidative degradation, hence for these drug substances impurity profiles, degradation levels and assay could be of high risk. (Table 4) represents the general initial risk assessment for supplier selection with Losartan Potassium as an API material.

Based on the above table, high risk parameters are impurity profile, residual solvents, isomeric purity, metal impurities, assay, polymorphism, particle size and bulk density. Further, a generic drug product manufacturer can request the suppliers to provide the information for pre-qualification questionnaire. Questionnaire should include supplier name, address, contact person, GMP facility inspections, approvals, warning letters (if any), recalls, delivery time, supply capability and initial high risk test items related etc. If pre-qualification information shows satisfactory results, then the generic drug product manufacturer may consider the supplier for further evaluation.

Document review: Generic drug product manufacturer should review the open part of the API DMF to understand the synthetic route, product specifications, analytical procedure, impurity profile, stability results, and amendments in the API Chemistry Manufacturing and Control part. API selection team should also consider the physical properties of the API such as particle size, bulk density, polymorphism, thermal behavior to assess and minimize the risk associated with generic drug product development. Starting materials and the synthetic process can influence the API quality and impurity profile and hence quality of starting material needs to be evaluated. Impurity profile is a key parameter for any API and hence the listed impurities and specified impurities of the API should be considered for evaluation [60-72].

Sample analysis: The analytical department team should analyze the API samples obtained from probable suppliers with the approved analytical test procedures. API samples from a minimum of three commercial scale batches should be analyzed by comparing the results of the analysis to the results of analysis of certified standard materials. Generic drug product manufacturer may analyze the API samples by implementing either the pharmacopoeial procedures (USP, Ph. Eur., JP or national pharmacopoeia) and/or in-house approved procedures. Additionally, the physical characteristics of the API such as particle size, bulk density, solubility, polymorphism and hygroscopicity should be evaluated. Finally, the analytical development team should prepare a comparison report based on the results of the analysis of API obtained from various API suppliers.

Onsite or off-site audit: Quality assurance (QA) team should prepare an assessment report on document review and analysis results. If these results are satisfactory then QA team can proceed for pre-audit documentation by providing the pre-audit questionnaire to the manufacturer. If an onsite audit is triggered then audit questionnaire can be sent to the supplier. If an onsite inspection triggered, then the inspection team should evaluate the API factory’s quality systems, deviations, CAPAs, recalls, warning letters, reprocessing batches, annual reports, CMC changes, batch to batch variability, OOS, OOT, specifications and pharmacopoeial adoption during inspection etc.

<table>
<thead>
<tr>
<th>Country Name</th>
<th>Acceptable format/quality</th>
<th>Pharmacopoeia</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>US-DMF</td>
<td>USP-NF</td>
</tr>
<tr>
<td>EUROPE</td>
<td>Approved CEP/EU-ASMF</td>
<td>EP</td>
</tr>
<tr>
<td>AUSTRALIA</td>
<td>Approved CEP/ASMF</td>
<td>EP/USP-NF/EP</td>
</tr>
</tbody>
</table>

Table 2: Regulatory agencies with DMF format and pharmacopoeia.

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Onsite or off-site audit: Quality assurance (QA) team should prepare an assessment report on document review and analysis results. If these results are satisfactory then QA team can proceed for pre-audit documentation by providing the pre-audit questionnaire to the manufacturer. If an onsite audit is triggered then audit questionnaire can be sent to the supplier. If an onsite inspection triggered, then the inspection team should evaluate the API factory’s quality systems, deviations, CAPAs, recalls, warning letters, reprocessing batches, annual reports, CMC changes, batch to batch variability, OOS, OOT, specifications and pharmacopoeial adoption during inspection etc.
QA team can complete these activities and present a final assessment report. If API facility is located within the same country/city then an onsite audit is preferred. In general practice, API supplier facility can be audited before the manufacture of the registration batches begins.

Summary data evaluation: Selection process results should be summarized for evaluation. Evaluation can be performed by adapting a risk based approach (risk assessment). Assessment shall be performed for all activities such as document review, sample analysis report and onsite/offsite audit results. A case study of the API supplier selection process is presented below to provide lucid description of the entire API supplier selection process and to put forth the primary responsibilities of the generic drug product manufacturer.

Case Study
Losartan potassium was selected as the API for evaluation and the below mentioned tables (Tables 5-8) summarize the risk based evaluation of different API suppliers of Losartan Potassium for various selection attributes such as finished specifications, supplier

Table 3: API selection core departments and responsibilities.

<table>
<thead>
<tr>
<th>Core Team</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical</td>
<td>Initial Assessment, Document review, Samples analysis, Impurity profile and Pharmacopoeial information and Risk assessment.</td>
</tr>
<tr>
<td>Formulation</td>
<td>Initial assessment, Document review and Results evaluation and Risk assessment.</td>
</tr>
<tr>
<td>Quality assurance</td>
<td>Initial assessment, Document review, onsite or Off-site audit and Samples analysis results and Risk assessment.</td>
</tr>
<tr>
<td>Regulatory Affairs</td>
<td>Initial assessment, Document review, Samples analysis results, DMF status, Pharmacopoeial information, Risk assessment and Patents related information.</td>
</tr>
<tr>
<td>IPR</td>
<td>Drug synthetic process, Polymorphism and Residual solvents</td>
</tr>
<tr>
<td>SCM</td>
<td>Administrative activities (purchase and logistics)</td>
</tr>
</tbody>
</table>

Table 4: Case studies-Initial risk assessment on Losartan Potassium API supplier selection.

<table>
<thead>
<tr>
<th>Test Item</th>
<th>Description</th>
<th>Identification</th>
<th>Loss on drying</th>
<th>Water content</th>
<th>Sulfated ash</th>
<th>Heavy metals</th>
<th>Residue on ignition</th>
<th>Limit test</th>
<th>Impurity profile</th>
<th>Residual solvents</th>
<th>Isomeric purity</th>
<th>Assay</th>
<th>Polymorphism (XRD)</th>
<th>Microbial analysis</th>
<th>Particle size</th>
<th>Bulk density</th>
<th>Thermal analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Item Initial Risk Assessment based on API</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>Low</td>
<td>Medium</td>
<td>No test</td>
<td>Medium</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
<td>No test</td>
</tr>
</tbody>
</table>

Figure 1: API selection process modules in generic drug product life cycle.
qualification samples analysis, open part DMF review observations and onsite or off-site audit results.

API Specifications

Specifications can indicate the API quality so it is mandatory to assess the risk of the API not complying with the prescribed specifications. Based on the open part DMF review API supplier finished product specifications can be assessed. Five selected suppliers’ risk assessment was completed and based on the risk assessment supplier-3 material specifications indicate tight specification limits.

Supplier qualification samples analytical results

Analytical testing methodology and results of the API suppliers’ qualification samples shall be evaluated for all API suppliers. It should be measured for all test items. Risk assessment results for five API suppliers are presented below.

Open part DMF review observations

If generic applicant wants to select the unregistered DMF material as API supplier then more activity should perform such

<table>
<thead>
<tr>
<th>Test Item</th>
<th>Supplier-1</th>
<th>Supplier-2</th>
<th>Supplier-3</th>
<th>Supplier-4</th>
<th>Supplier-5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDENTIFICATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>XRD</td>
<td>Low</td>
<td>No test*</td>
<td>Low</td>
<td>No test*</td>
<td>Low</td>
</tr>
<tr>
<td>HPLC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Other (UV, Chemical etc.)</td>
<td>Low</td>
<td>No test*</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Water content</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>No test*</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Limit test</td>
<td>No test*</td>
<td>No test*</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Impurity profile</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Residual solvents</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Isomeric purity</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Assay</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Polymorphism (XRD)</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Microbial analysis</td>
<td>No test*</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>No test*</td>
</tr>
<tr>
<td>Particle size</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Bulk density</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Thermal analysis</td>
<td>Low</td>
<td>No test*</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table 5: Risk assessment on basis of API attributes.

<table>
<thead>
<tr>
<th>Test Item</th>
<th>Supplier-1</th>
<th>Supplier-2</th>
<th>Supplier-3</th>
<th>Supplier-4</th>
<th>Supplier-5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDENTIFICATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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</tr>
<tr>
<td>FT-IR</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>XRD</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>HPLC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Other (UV, Chemical etc.)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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</tr>
<tr>
<td>Loss on drying</td>
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<td>Low</td>
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<tr>
<td>Water content</td>
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<td>Medium</td>
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<td>Low</td>
<td>Medium</td>
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<tr>
<td>Sulfated ash</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Heavy metals</td>
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<td>Medium</td>
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<tr>
<td>Residue on ignition</td>
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<td>Limit test</td>
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<tr>
<td>Impurity profile</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
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</tr>
<tr>
<td>Residual solvents</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Isomeric purity</td>
<td>Medium</td>
<td>Low</td>
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<tr>
<td>Assay</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
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<tr>
<td>Polymorphism (XRD)</td>
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<tr>
<td>Microbial analysis</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Particle size</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Bulk density</td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Thermal analysis</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
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</tbody>
</table>

Table 6: Risk assessment on basis of suppliers samples analysis.
as comparison of other approved API DMF synthetic route, impurities profile, residual solvents, analytical reports (spec, mos, method validation, stability etc.) and physicochemical properties. Regulatory perspective, generic application approval may delay due to DMF and generic application review and facility inspection. Open part DMF/ ASMF/CEP should be reviewed carefully for all sections of drug substance. DMF review report should be prepared by all core departments and comparison report also prepared for all API suppliers. Based on the comparison results risk assessment can be performed as per below table.

**Onsite or offsite audit evaluation**

API supplier selection process covers onsite or offsite audit of the API manufacturing facility. Onsite audit will be handled by either the personal team or third party inspection team. Onsite audit or Offsite audit report can include evaluation results of GMP quality system and API material specific. Based on the all API supplier’s evaluation report risk assessment can be performed.

**API supplier approval or rejection**

This is last step in the process of API supplier selection. (Tables 3-6) represent all API material sample analysis results, DMF document observations and inspection results. Above steps and the evaluation results revealed that supplier-3 had produced API of high quality in a GMP compliant facility. Finally, supplier-3 was selected as the main supplier for the API and another supplier was selected as an alternative API supplier. If any quality or administrative disputes would arise in due course of time with the first API supplier, then the generic drug product manufacturer may have an option to consider the already selected alternate API supplier or even a new supplier appropriately.

**Module-2: Product Development Phase**

Generic drug product development proceeds with QbD approach. QbD elements and tools are QTPP (quality target product profile), CQA (critical quality attributes), CMA (critical material attributes), CPP (critical process parameters), DoE (design of experiments), DS (design Space) and CS (control strategy). Drug product development steps include pre-preparation, lab scale, pilot scale and pivotal scale (exhibit batch). Figure-3 represents the generic drug product development steps. If any there is a change or addition of an API supplier in any of these steps then the generic drug product manufacturer must perform re-development experiments. Table 9 has listed the development steps and re-development activities.

**Module-3: Post Drug Product Development**

**Module-3A: Drug application review phase**

Generic drug product application shall be submitted to the health authority in the CTD format. Generic drug product manufacturer can submit the application in the CTD format for multiple APIs (sourced from different manufacturers) as well. If the API is obtained from an alternative supplier then the generic drug product manufacturer should manufacture separate batches of the drug product using API obtained from the various API suppliers. Generic drug product manufacturer will also need to have in-vitro comparisons, equivalency reports and stability data for the drug product manufactured from the API obtained from various API suppliers. During the regulatory review phase for the change or addition of the API supplier, the generic drug product manufacturer has to communicate to the regulatory agency to initiate the change of switching to an alternative API supplier. USFDA has published the guidance “Alternate Source of the Active Pharmaceutical Ingredient” in Pending ANDAs that clearly discusses the regulatory requirements for alternative API source for the US market.

**Module-3B: Post product approval**

After approval of the generic drug product by the health authorities, the API supplier may be changed or a new API supplier may be added by the generic drug product manufacturer. Such API supplier changes have to be addressed by referring to the SUPAC guidelines for the USA market and the variation procedure guidelines for the EU market. Regulatory agencies demand to have complete report on the synthetic route of the APIs obtained from the previous and new API suppliers, impurity profile, starting material, residual solvents, polymorphism, physical properties (bulk density, particle size, Hygroscopicity etc.), product specifications and analytical test procedures, in vitro dissolution reports and new batches with new API material. Stability studies and requirements are similar with submission batches.
Case studies

All the regulatory authorities across the globe possess more or less similar expectations from drug product manufacturers for API supplier change or addition. API synthetic process and control of drug substance are the key elements from regulatory perspective. General case studies (not limited to these) on API supplier change or addition are tabulated below.

API Supplier Impact on Generic Drug Product

Generic drug product manufacturers should carefully monitor the API supplier selection process and also observe API facility quality and inspection issues throughout the generic product life cycle. Presented below are some hypothetical illustrations proposing the possible impact API supplier selection process may have on the generic drug product.
Impact on ANDA approval

A generic drug product manufacturer has submitted application to the agency and agency review completed waiting for final approval. Meanwhile API manufacturer (supplier) has faced the regulatory GMP inspection and it was failed. Inspection failure happened due to non-compliance of GMP practices, procedural compliance and product quality issues. API supplier was received the import alert from regulatory agency. Finally API facility re-inspection was delayed one year and ANDA application was approved by one year.

Drug product market revenue

A generic drug product manufacturer has developed, submitted to agency for approval which has market value 100 million USD per year. Review was completed and waiting for agency approval but due to quality issues in API facility regulatory body ban the products from this facility. Finally the generic approval has delayed about fourteen months. After generic approval the market value comes down about 60 million USD per year due to other player’s entry in to the market. Here API manufacturer has influenced the generic player profit. So API supplier selection plays key role in the generic product life cycle. Continuous monitoring should be required on API manufacturer’s quality, recalls and inspections.

Conclusion

API supplier selection has been considered to be a significant aspect of the generic drug development process for the generic drug product manufacturer to obtain a drug product of high quality and one that complies with global regulatory requirements. Generic drug product manufacturers with their own API production capacities may not be involved into API supplier changes. However other generic applicants should proceed with scientific approaches including appropriate risk assessment on API characteristics, critical quality and material attributes. This article presents technical information, regulatory discussion and case studies on primary and alternative API selection process and procedures. Generic drug product manufacturer may change the API supplier in the development phase as well as in the post development phase. If the API supplier change happens in the development phase then a scientific justification needs to be adequately captured in the product development sections of CTD. (Table 10) For post approval API supplier changes or addition of API suppliers; the regulatory path for seeking approval of the new API supplier is relatively stringent and closely scrutinized by the health authority. All these post approval activities shall be handled with SUPAC for USFDA/ variation filing for EMA applications.

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