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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. Contradictorily, 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 aversive 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 discerning 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 manufactures 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

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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

GMP failures	Inspection findings
Laboratory controls	Lack of or inadequate method validation, online documentation, scientific and appropriate specifications/analytical procedures; failures of adequate investigations on out-of-specification (OOS) and out-of trends (OOT); failures of adequate stability testing programs to assess the quality attributes.
Quality system	Failure of the quality unit to release/reject APIs, scrutinized review of quality-related documents; failure in investigations, quality reviews of the APIs and handling of APIs CMC changes.
Equipments	Maintenance, cleaning procedures, validation of cleaning procedures, cleaning, store and sanitization for contamination or carryover.
Records and reports	Failures in batch records preparation; establishment of written procedures related to production, quality, laboratory controls, and material management.

Table 1: Common GMP inspection finding in recent years.

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 in to three classes. Class-1: Solvents to be avoided; class-2: Solvents to be limited; and class-3: Solvents with 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 test 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 that would not be treated by either the other stereoisomer or the racemic mixture of the same API. This therapeutic selectivity of stereoisomers of an API should be considered by the generic drug product manufacturers when opting for a specific API supplier. Isomeric form content can be determined by using SOR or by HPLC methods. Generally, isomeric form conversion during the drug development phase is a rare phenomenon [39,40].

Hygroscopicity: Some of API materials are very hygroscopic in nature and the hygroscopicity can influence the drug product quality and impurity profile. For such hygroscopic APIs, the supplier selection team should consider this attribute as critical quality attributes [41-45].

Solubility: API solubility can influence the drug product quality attributes such as dissolution, disintegration, impurity profile and bioavailability etc. Generic drug product manufacturer should evaluate the API solubility during (in different buffers across pH range) the supplier selection and product development phases [44,45].

Bulk density/Tapped density: Bulk/Tapped density can influence the flow property of the granules in generic drug product manufacturing process. Bulk density is one of the critical quality attributes and critical material attribute (CQA and CMA) influencing the drug product manufacturing process. Flow property has direct impact on content uniformity, dissolution, and uniformity of dosage. Specifications of Bulk/Tap Density depend on the formulation so the specification limits may vary for the drug product manufactured by one generic drug product manufacturer to another [46,47].

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.). Generic 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

Country Name	Acceptable format/quality	Pharmacopoeia
USA	US-DMF	USP-NF
EUROPE	Approved CEP/EU-ASMF	EP
AUSTRALIA	Approved CEP/ASMF	EP/USP-NF/BP

Table 2: Regulatory agencies with DMF format and pharmacopoeia.

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 finalize the selection process and should actively be involved in the initial product risk assessment, document review, results review, onsite or offsite audit, and risk assessment [55-59].

Intellectual Property Rights (IPR) Team

IPR 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 offsite 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.

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

Table 3: API selection core departments and responsibilities.

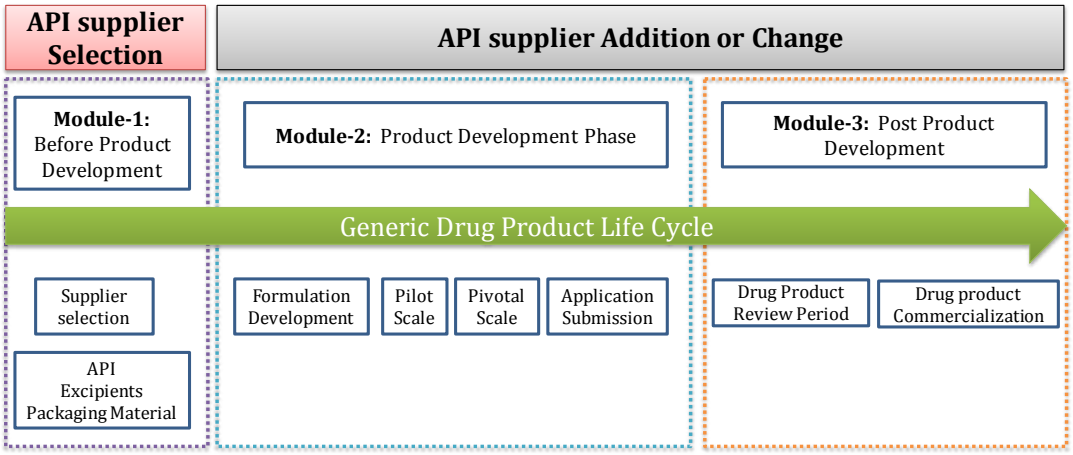

Figure 1: API selection process modules in generic drug product life cycle.

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

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

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

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

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

Table 5: Risk assessment on basis of API attributes.

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

Table 6: Risk assessment on basis of suppliers samples analysis.

CTD Section (Module-3)	Supplier-1	Supplier-2	Supplier-3	Supplier-4	Supplier-5
3.2.S.1 General Information	Low	Low	Low	Low	Low
3.2.S.2 Manufacture	Low	Low	Low	Low	Low
3.2.S.3 Characterization	Low	Low	Low	Low	Low
3.2.S.4 Control of Drug substance	Medium	Low	Low	Medium	Low
3.2.S.5 Reference Standards	Low	Medium	Low	Low	Medium
3.2.S.6 Container closure system	Medium	Low	Low	Low	Low
3.2.S.7 Stability studies	Low	Low	Low	Low	Low

Table 7: Risk assessment of suppliers open part DMF document review observations.

Audit	Supplier-1	Supplier-2	Supplier-3	Supplier-4	Supplier-5
Administrative	Medium	Low	Low	Low	Low
Manufacturing related	Low	Medium	Low	Low	medium
Product recalls	High	Low	Low	Medium	High
Inspection failures	Low	Medium	Low	Low	Medium
CAPA	Medium	Low	Low	Medium	Low
Facility capacity	Medium	High	Low	Medium	Low
Recent manufacturing changes	Medium	Low	Low	Low	Medium
Recent specification changes	Medium	Low	Low	Medium	Low

Table 8: Risk assessment for audit observations.

as comparison of other approved API DMF synthetic route, impurities profile, residual solvents, analytical reports (spec, moa, 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-formation, 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.

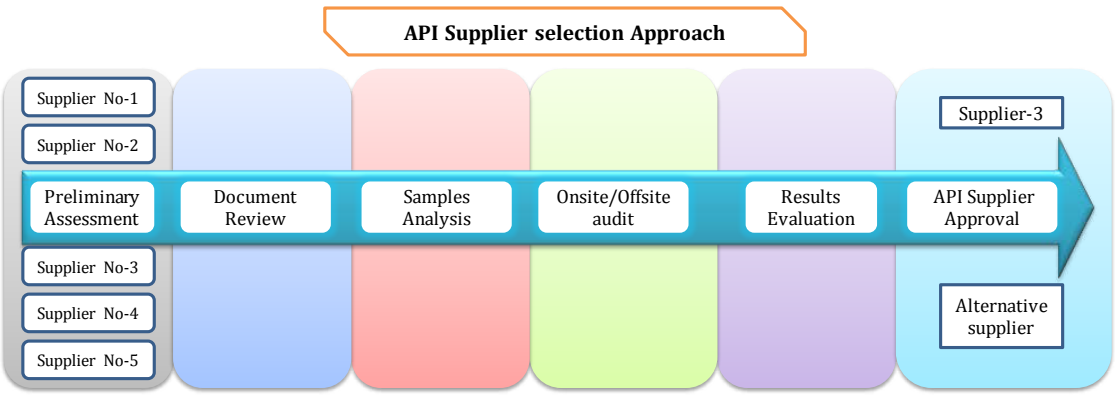

Figure 2: API supplier selection process (Module-1).

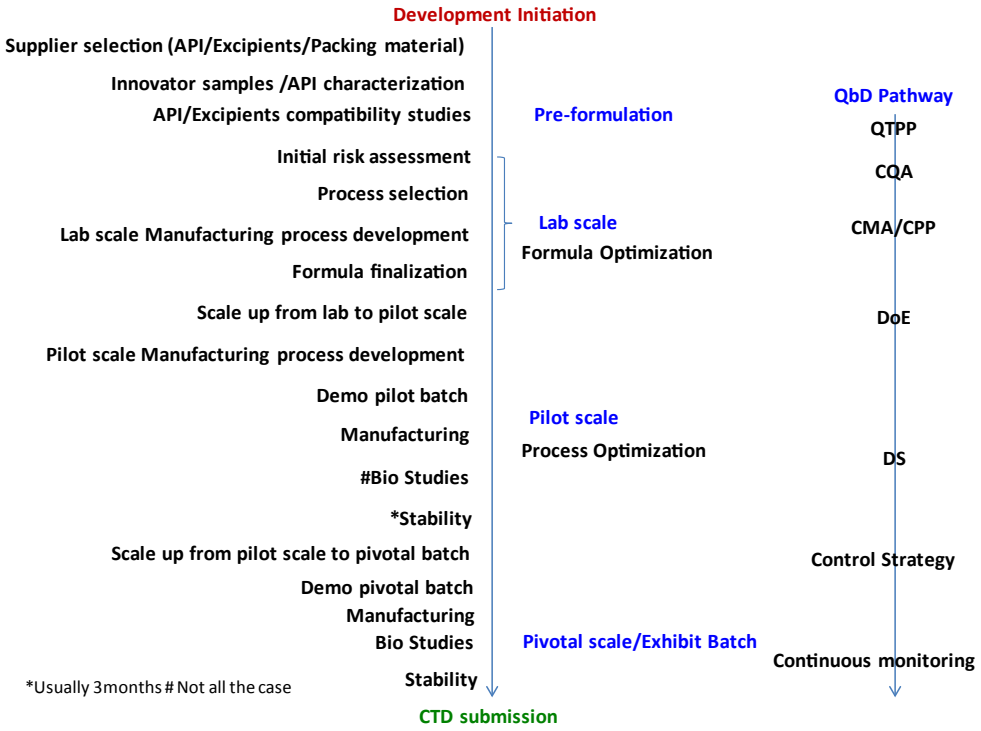

Figure 3: Generic drug product with QbD pathway.

Generic development stage	Completion of activity	API supplier change Re-work
Pre-formulation	API characterization, Excipient compatibility, QTPP	Excipients compatibility
Lab scale	CQA, CMA, Initial formulation development experiements, DoE, Lab scale stability	Excipients compatibility, QTPP, CQA, CMA, DoE
Pilot scale	Pilot process development, pilot scale bio studies, Stability	Excipients compatibility, QTPP, CQA, CMA, DoE and Stability studies
Pivotal scale (Exhibit batch)	Pivotal batches manufacturing, bio studies and Stability	All formulation development activities

Table 9: Generic drug development stages and API supplier change requirments.

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.

Development Step	Regulatory Expectations
Case-1: Concern on polymorphic form change/ Bulk density/ Particle size	
After completion of excipients compatibility	Comparison report on excipient compatibility and polymorph characteristics between both the suppliers. (Could be considered as an Internal document part of Quality system). Risk assessment report on both API materials.
After lab scale completion	Comparison report on excipient compatibility and polymorph characteristics and other drug product critical quality attributes (Based on the Risk Assessment of drug substance properties on drug product CQA) (Could be considered as an Internal document part of Quality system). Risk assessment report on both API materials.
After pilot scale completion	Comparison report on excipient compatibility and polymorph characteristics and other drug product critical quality attributes (Based on the Risk Assessment of drug substance properties on drug product CQA). Risk assessment report on both API materials.
From pivotal (exhibit)scale manufacturing to 6months stability study	Redevelopment. Bio studies are required on new API supplier.
Case-2: Concern on API supplier market recalls or warning letters or GMP facility observations	
After completion of excipients compatibility	Compatibility studies need to perform with new API
After Lab scale completion	Compatibility studies, QTPP and lab scale trials need to perform with new API
After pilot scale completion	Compatibility studies, QTPP, CQA, CMA and lab scale trials, process optimization experiments need to perform with new API
From pivotal (exhibit)scale manufacturing to 6months stability study	All developmental activities (Compatibility studies, QTPP, CQA, CMA and lab scale trials, process optimization, pivotal batches mfg. bio studies and stability) need to perform with new API
Case-3: Alternative API supplier adoption	
From development initiation to pivotal batches mfg. and 6months stability completion	QbD activities such as QTPP, CQA, CMA and CPP need to perform with new API. One pivotal (exhibit) batch need to manufacture and in-vitro dissolution, stability data should be submitted along with the generic application.
After generic application submission (review and post approval)	Comparison report on both APIs. One or two pivotal (exhibit) batches and in-vitro dissolution (release/multimedia), stability data should be submitted along with the generic application.

Table 10: Case studies for API supplier change or addition.

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 60million 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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