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Five issues to consider in API sourcing before they become a problem

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ABSTRACT

API sourcing is a very complex process and there are many chances for things to go wrong.
In this article we look at some common issues which, if not understood and managed in advance, can turn into problems later: communication of known requirements and checking of manufacturer capabilities; the often neglected concept of 'partnership'; some recent transportation issues and finally the importance of working with suppliers that want your business - and how to spot those that don't.

In this world of internet shopping and next day deliveries 'supply' has become synonymous with 'delivery'. We don't have to concern ourselves about the process that leads to the delivery, just whether we will be in the house when the courier arrives with our new USB cable or t-shirt.

In great contrast, 'supply' of an active substance is a long complex process. It consists of many stages and we must accept that the final delivery of some drums of white powder is the last, very small, part of a whole package of technical, commercial, regulatory and service elements. Successful API procurement requires you to be aware which of those elements might affect your ability to receive your material. Risk mitigation is not an abstract concept here as we can often make choices earlier on to avoid problems later, and backtracking to fix an earlier bad decision can be expensive or even impossible.

A key realisation after many decades of raw material supply is that not every manufacturer is 'right' for every customer. They make it; you need it... Voilà? No, it's more nuanced than that, and we examine some of the issues here.

When we look at the web of interconnected issues that are wrapped around API supply and that all need to be right for the business to happen, the complexity becomes apparent. It is critical that buyers adopt a strategic approach from the very beginning and think many moves ahead in the procurement process. The good thing is that you should know what the moves are going to be. The surprising thing is how often they get forgotten...

1 Clear and open communication

Do not be guilty of failing to communicate known requirements in advance. Think ahead to what you will need and say it - don't drip feed the information in

First questions should be what do you need the API for and where do you intend to sell your finished product. If it is for a product intended for the US, then US FDA registrations for the establishment and the DMF must be in place. There is no point to start working with a source that you will not be able to use later. It sounds so obvious but people do make assumptions and unless you ask the supplier the specific question you cannot be sure. Get a confidentiality agreement in place if you want but in general there's more to be gained by sharing than by keeping everything secret.

If you need the material for an EU product, then going with a CEP source will make your regulatory submissions much easier than choosing a factory that only has a DMF. Obviously the EDQM CEP database (1) is your first place to check options, but that could be only the beginning. A few random mouse-clicks as of June 2019 show 22 valid CEPs in place for Atorvastatin, 19 for Simvastatin, 19 for Sildenafil... How to choose between sources if you want one of these APIs? You must choose the source that is right for you.

Generally speaking, it's a relatively level playing field for manufacturers in that everyone ticks the GMP box; everyone meets the Pharmacopoeias; 'rogue' sources have largely been regulated out of regulated markets. Of course, any specific technical requirements on the API have to be right as well as all the hard factors such as production capacity; physical availability etc. But you should also think ahead to the regulatory support you will need and those awkward regulatory requests: do you need the open part of the DMF, the impurities, an audit slot before the planned launch as your company doesn't accept third party reports...?

So how do you know if a source is right for you? By communicating your requirements early in the sourcing process. Don't drip-feed information in to your supplier

and then be surprised when something you did not ask for earlier is not possible.

Everyone everywhere wants to know 'how much does it cost…' but that's now, not necessarily in two or three years when your project becomes commercial and there are so many more questions to ask first. Failure to communicate basic known requirements in advance coupled with a fixation on very 'moveable' elements such as price is a very common instance of a poor strategic approach to choosing a new source.

2 The cogs must ALL fit together

API manufacturers don't have infinite flexibility in campaign scheduling, batch availability, non-standard PSD samples. Your needs must align with their capabilities. You must check.

Campaign production would be a good example of where things can go wrong for new projects. Many APIs are produced at multi-API sites where production is planned to approximately meet with existing customers' forecast demand requirements. If you are a new customer your demand will not have been included. Campaigns could be once a month or once a year – you won't know until you ask. If you know you will need three batches of API to manufacture three submission batches of finished product you must align your procurement with the R&D work and submission timeline of your regulatory affairs team and batch availability. It may be the case that the API manufacturer has stock of material from one batch but availability of the other batches could be many months away, completely derailing your submission planning.

It is thus crucial not to make any assumptions about the API manufacturer's production situation or likely lead time for supply – this must be checked. If you have a choice of suppliers, one of whom manufactures more frequently, then you will probably save yourself trouble later by choosing them. In fact, it's not a bad idea to get a feel for how important the API is to the manufacturer – be careful if it looks like you are the only customer.

Non-standard Particle Size Distribution (PSD) requirements are another particular hazard. The over-enthusiastic sales person will always tell you they can supply any PSD requirement you have, and no doubt they can for commercial quantities. But for the small quantity of three batches that you need for development? Micronizing small quantities is always a problem: difficult and expensive because the sample size required by the development team is usually much smaller than can be easily micronized. The API manufacturer will probably have waste and losses and will be distinctly unenthusiastic to supply. If you only have a choice of one source then you will just need to work this out. If, however, you have two possible suppliers, one of whom already has a standard micronized grade that you might be able to use, they should become automatic first choice as there will be far fewer availability head-aches.

3 Accept the partnership concept

The API manufacturer is your partner for the manufacture of your product: you rely on each other. Do you think of them as a partner? Or as a supplier? Or as the enemy?

On the commercial side, what about price – is that an issue that can become a problem? Perhaps less for the reasons you might think. Procurement people generally seek to reduce the direct spend but there's a balancing act on this and one of the biggest potential losses you will face relating to API supply will be if you don't have any material, and can't make and sell your product. The arguments over a few percent price rise are trivial in comparison.

We see more direct examples of projects failing, or supply drying up, because of low API prices compared to the opposite: high prices making a finished product uncompetitive. The reasons are easily understood: the API manufacturer probably makes a whole list of products. If their returns on the product you buy are too low – or comparatively lower than other products that can be made using that same production line - they will obviously be less keen about your business.

This illustrates a largely under-acknowledged aspect of a successful supply chain: the API manufacturer and the medicines manufacturer are partners. Each relies on the other. The API source is however rarely considered the 'partner', far more usually the 'supplier'. This brings a different psychological approach which can easily become: 'we are the customer, we are right'. This attitude risks losing sight of issues facing the supplier and, in a partnership situation, 'your problem' very quickly becomes 'my problem'. In one memorably bad-tempered email exchange we had following a sudden 300% API price rise:

"The situation is changed, now as we are going to discontinue production after 1st Quarter 2018. We confirm our quotation of Euro 2.000/Kg for 10 Kg. If you are not interested, drop the matter and do not disturb [us] anymore.
Best regards." (2)

In this case, the customer paid the higher price and was forced to approve a new source. Perhaps if the manufacturer had discussed a higher price earlier then they might not have needed to stop production. Everyone fights higher prices – this is a given – however the cost of change control to move to a new API source, in addition to the increase in risk and potential disruption to the business that this brings, puts a different light on that price discussion. The above example illustrates a compartmentalization of the players in the supply chain where there was no partnership and each party came to decisions in isolation. End-user and API manufacturer have effectively become enemies, the supply breaks down and everyone loses.

Thus, while it may be considered 'procurement heresy' you could consider paying more for the API than they offer – especially for lower volume procurement. Everyone is your friend for 20 tonnes but not everyone is your friend for 20 kilos and it is simply not the case that every API manufacturer will welcome every enquiry. Sales people the world over agonise over how to set pricing for smaller quantities and we see examples where the price for a few kilos is only slightly higher than for tonne lots. Too cheap! If you see this you may not be getting a bargain: they won't be happy supporting the regulatory and if they're not happy, the service you get will be miserable. Or worse, supply might stop. Remember the 'supplier' vs 'partner' issue: you need their support and your long-term interests might not be best served by getting a 'killer price' today.

4 Transportation

Many Technical Agreements haven't caught up with the guidelines for GDP for Active Substances. Check yours for subcontracted activities within the logistics chain and API transport conditions

Shipping and logistics have traditionally run fairly smoothly and most problems were in the 'unpredictable' category. The Falsified Medicines Directive (2011/62/EU) brought all players in the supply chain under the regulatory umbrella and the subsequent 2015 Guidelines for Good Distribution Practice for Active Substances (3) provided the rules of the game, so we can now start to see where issues might arise.

'Subcontracted activities' is one area to look at. The GDP guidelines (4) require written agreements to be in place where storage or transportation is contracted out. If you are buying APIs from either a distributor or the manufacturer directly you should check your supply chain security statements either specify the named, approved third party logistics partners or at least give a confirmation that written agreements are in place with these service providers.

"Don't we have responsibility only as long as material is on our premises / warehouse?" (5)

We have had experience of more than one manufacturer believing that the GDP guidelines do not apply to them but unless they only sell 'ex-works' this is not correct. If any element of the transport process is arranged by the API manufacturer then they become a distributor and GDP rules therefore apply as clearly stipulated in the introductory section of the guidelines (6).

Chapter 6.14 of the guidelines covering transport conditions for APIs is another point that appears to be attracting greater attention, certainly in the UK. Traditionally, transport conditions were accepted to be per Section 14 of the material's Safety Data Sheet and if there were no special conditions it meant no special conditions. This is not now recognized, by the MHRA at least, and specific transport conditions are required from the API manufacturer even for those APIs with no specific transport conditions.

This seems to be crystallizing towards 'material should be shipped within a temperature range for which long term stability data is available' with additional data to be relied on for any excursions. The API manufacturers and the medicine manufacturers are being pushed on this on inspection. This is Technical Agreement territory which might have been a little thin on the transport conditions in the past but it is being pulled up now.

The problem of course is evidencing temperatures during the supply chain and despite very little appetite from industry for something which was never considered to be a problem, the end-point of the regulatory logic would be data-loggers, or temperature controlled, for every shipment of everything.

Long term stability data is unlikely to be over 40°C and this does not even cover recent European summer heat-waves, let alone domestic haulage in India for example. However, in a recent request to manufacturers for specific transport conditions for over 100 APIs, the majority of the statements came back providing *storage* conditions based on long term or accelerated stability data at that 40°C level. This is insufficient and manufacturers must be prepared to be challenged on this. Risk assessing the transportation with a view to avoiding the extra cost and complications of data-loggers, a manufacturer statement confirming API stability at higher temperatures from, eg, a Forced Degradation study could provide better confidence. Better still, manufacturers might consider designing stability tests specifically for transport based on potential risks not expected in normal storage, such as repeated temperature bounces. The transport conditions story isn't over yet.

5 Evaluate and establish good relations

'Soft factors' (ie the people you must work with) are important. Select an API supplier that is interested and responsive to your needs. Judge this from the earliest communications.

When you are choosing a new supplier, if all the 'hard factors' such as production capacities and campaign schedules between alternative source options are equal, then it is the 'soft factors' which assume a greater importance. This means the people you must deal with and the structure within which they have to work.

The extra significance in the world of supply for APIs is that the relationships are often monogamous. Single sourcing, for all the negative strategic consequences that this might have, is nonetheless prevalent. Enormous amounts of time, effort and money are required for approval of a source and therefore the care that goes into the selection process of Factory B over Factory A must reflect the importance of the final decision.

How can you assess the soft factors? From your first contact with potential suppliers you should start judging the replies. The initial contact should be short and simple: you have a requirement for the product, are they making it, can they supply, who is the right contact to discuss in more detail. Now, how long did you have to wait for an answer? If they can supply, they will invariably want to know how much you need, so after you give them a rough indication of volumes how enthusiastic do they seem to be for your business? Judge these responses and trust your instincts: if it already feels like hard work talking to them, a little amber light should start blinking in your mind.

As you develop the conversation, don't stop judging: how hard is it to get answers to your questions? Do they miss things out without referencing the omission and you have to chase? Does it take a ten email exchange to agree a Confidential Disclosure Agreement? Does it feel like you are the first person in the world to request a TSE statement? This all matters because it is an indicator of how smooth things are likely to be as the project progresses and turns into a business. You will rely on your contact to provide the documentation and information that you absolutely need.

Do your regulatory requests have to pass through the commercial team at the API manufacturer? We see this a lot. Consider that a producer with say 30 or more APIs, selling to multiple customers in multiple countries will have an exponential number of completely standard regulatory requests from all those customers – all just as important as your requests. It can lead to significant bottlenecks in the document flow when the requests are handled by the same people who are principally trying to sell the products. It varies company to company, but try to deal directly with the regulatory affairs team if you can. And manufacturers: it is false economy to restrict staff numbers on regulatory service support. This is a critical part of the total supply picture and a reputation for bad service is absolutely taken into consideration when customers are considering where to place their business.

If you only have a choice of one source for your API, then at least be aware of these issues and proactive in managing the supplier.

If you have a choice of several manufacturers then factor these issues into your initial sourcing assessment matrix. If all

else is more or less equal (and you know this because you have strategically and carefully asked the same questions to your final short list of potential sources) then choose the supplier who is most interested in your business. This is the one with whom you are most likely to be able to form a good, functional, partnership-type relationship.

The conclusion may seem obvious, but you can only reach this conclusion by doing the hard work in the beginning. Rest assured however, that any such hard work will be far less than trying to dig yourself out of a big hole if things go wrong later!

REFERENCES

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ABOUT THE AUTHOR

*Owner and MD of Wessex Fine Chemicals Ltd, **Nick** has been supplying raw materials to the pharmaceutical industry since 1988. He became very actively engaged with the regulatory process after 2011/62/EU revealed a deep lack of understanding across the industry about what it would really mean for API supply. Now successfully MHRA registered and GDP inspected, Nick strongly believes that if no one can tell you the answer, you better go find out for yourself.*