



CHEMAGIS LTD.
31 LEHI STREET
P O BOX 31, 51100 BNEI BRAK, ISRAEL
REGULATORY DEPARTMENT:
TEL: 972-3-5773664; FAX: 972-3-5773689

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Re: Docket no. 2003 D-0571

Dear Sir or Madam,

Please find hereunder Chemagis Ltd. comments on FDA's Draft Guidance for Industry:
" Drug Substance – Chemistry, Manufacturing, and Controls Information " (January
2004).

Sincerely,

Berta Weitman
Regulatory Affairs Manager
CHEMAGIS LTD.
31 Lehi St., P.O.Box 31
51100 Bnei-Brak, Israel

Tel: 972-3-5773-664
Fax: 972-3-5773-689
e-mail: bertawn@agis-group.co.il

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DRAFT GUIDELINE

In January 2004 the FDA has published a draft guideline for the industry named "Guidance for Industry, Drug Substance, Chemistry, Manufacturing and Control Information".

In general, this guideline is a large leap forward from the old 1987 guideline. A long time has passed and changes in the industry were enormous in that period. However, there is one issue, in which we respectfully disagree with the agency. In this draft guideline the agency deals with the definition of the term "starting material" suitable for producing an API considered to be a synthetic drug substance. A long discussion is given in attachment 1 to this draft guideline (pages 48-55; lines 1666-1988). Similar arguments may also apply to starting materials of plant or animal origin (see attachment 2) but for the sake of simplicity and shortening this document we shall focus on the first case only.

The source of the issue of choosing the starting material is the fact that while the API manufacturers are routinely inspected and regulated by the agency to ensure the quality of the API, this, in many instances, is not the case with the production of earlier stages in the chemical process that finally ends up with the API at hand. The agency suspects that lack of control (or having limited control) on the earlier stages of the process might have an adverse effect on the API. This is best phrased in lines 1678-1681: "Because there is limited FDA oversight of the manufacturing of the starting material, the starting material should be selected and controlled so that the risk from future changes in the quality of the starting material affecting the identity, quality, purity or potency of the drug substance is minimized". This fear is not totally relieved by ICH Q7A guideline, because this guideline uses qualitative terms that state that the level of GMP should be deeper when we approach the drug substance stage.

While this issue is correctly raised the solution offered by the draft guideline will not necessarily obtain its goals. At the same time it loads unnecessary burdens on the Industry's back. I would like to analyze the discussion depicted in the draft guideline, show the problems embedded in it and suggest, at the end, a different approach.



ISSUE 1: STARTING MATERIAL HAVING SIGNIFICANT NON PHARMACEUTICAL MARKET VS. ONE NOT HAVING SIGNIFICANT NON PHARMACEUTICAL MARKET.

Motto: Your neighbor's lawn is always greener.

The draft guideline divides the starting materials to those which already have a significant non pharmaceutical market and those that do not have a significant non pharmaceutical market. The first type is automatically considered as suitable starting materials to start the chemical process for the drug substance. The existence of a significant non pharmaceutical market is considered a sufficient justification for choosing this compound as a starting material. The guideline argues that manufacturers of such starting materials have the expertise and long term practice to manufacture them in a consistent quality. This thesis may be right sometime, but it cannot be always valid. Non pharmaceutical markets are sometimes (though not always) characterized by total lack of quality systems during the process in which the suggested starting material is produced, or worse, also in the process from this starting material to the marketed product (whatever it is). The drug substance market in the US is strongly regulated and heavily inspected to ensure the quality of the products. Total reliance on the mere fact that there is a significant non pharmaceutical market as assurance for the starting material quality is liable to lead to disasters. Indeed, the quality of the starting material is the responsibility of the API producer, but this approach encourages shirking from this obligation.

In reality, there are many less regulated markets for pharmaceutical products. Most of these countries also do not abide, or only partially abide intellectual property rights. As a result, in these countries one can find generic versions of finished dosage forms many years before the regulated market (US as an example) turns generic on this specific drug. Therefore, you can find reliable suppliers, more importantly, reliable suppliers with lots of experience in this product and its precursors for a chemical that is needed solely for pharmaceutical use. Their experience can be as good as any supplier for the non pharmaceutical markets.

Even worse, the draft guideline declares (lines 1701-1705) that if the commercial starting material that has a significant non pharmaceutical market is of inferior, unsuitable quality, the API manufacturer is allowed to upgrade and improve the material quality in its premises. This purification needs to be incorporated in the documentation. Now, upgrading is allowed in this case but is not allowed in cases where the non pharmaceutical market is not there. The chances that the manufacturer of the starting material is much more controlled by the API producer when this is a relatively new compound are much higher. The control on a non GMP non pharmaceutical material producer is much weaker, if there is some at all. Remember, the pharmaceutical market is usually the non significant one since only limited quantities are needed. Control and influence on the supplier in this situation are weak to nil.

Control of the quality and consistency of quality of starting materials are very important, but relying on the non pharmaceutical market is not an appropriate solution.



ISSUE 2: SELECTION PRINCIPLES

In lines 1730-1733 of the draft guideline the 2 goals to meet with the aid of the selection principles are:

- Sufficient information is submitted to the FDA to evaluate the safety and quality of the drug substance.

I cannot agree more. This is an important part of the essence of the regulatory work.

- Future changes in the starting material, or changing supplier are unlikely to affect the safety and quality of the drug substance (as long as compliance with the specifications is kept).

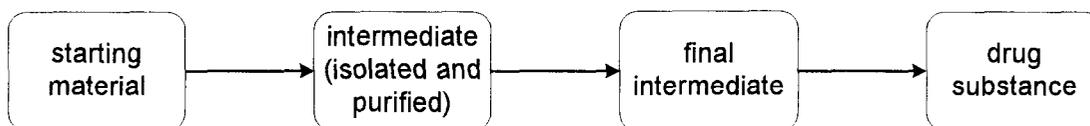
This sounds nice, but in reality it is far fetched. No chemical process will 100% guarantee that any future starting material that meets the specifications will lead automatically to a good quality drug substance. Ask any professional chemist in the API industry, you will get the same answer.

In order to achieve these goals the draft guideline describes in detail 4 selection principles for starting materials (without significant non pharmaceutical market). These are propinquity (lines 1740-1766), isolated and purified (1768-1773), carryover of impurities (lines 1775-1797) and complexity of structure (1799-1818).



ISSUE 3: PROPINQUITY

According to this selection principle the starting material should be separated from the final intermediate by several reaction steps that result in **isolated and purified** intermediates. If we take the minimal several as two it means that the API manufacturer is requested to carry out at least 3 chemical steps. This is described in the scheme.



The rationale behind this is that the chances of an impurity (old or novel) to be carried all the way to the drug substance are smaller if the process comprises of more steps (lines 1748-1751).

While in many cases it is correct, this is not always the case. We would like to give a real example.

Fluticasone propionate (6 α ,11 β ,16 α ,17 α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester) is made in 5 chemical steps from flumetasone ((6 α ,11 β ,16 α ,17 α)-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione). If the flumetasone starting material is contaminated with a 6-chloro analog (chlorine instead of fluorine) the fluticasone propionate obtained is contaminated with exactly the same amount of the fluticasone propionate 6-chloro analog. Five chemical steps and several additional purification steps did not decrease the level of the 6-chloro analog at all.

Purification of the intermediates is also believed to be a good means of getting a better quality of drug substance by holding a higher grade of intermediate. Again, while this is the case in many instances, it is not needed in all cases. As an example let us look at the fenofibrate process. In this process 4-chlorobenzoyl chloride is reacted with anisole in the presence of anhydrous aluminum chloride to give 4-(4-chlorobenzoyl)phenol. This is further reacted with 2-bromo-2-methylpropionic acid isopropyl ester to yield fenofibrate. In the first step, a side product, 2-(4-chlorobenzoyl)phenol is formed in the amount of ~10%. When the intermediate is precipitated, its amount is decreased to 0.5-1% of the intermediate. Should the intermediate be purified? The answer is no. we have shown that the process gives fenofibrate drug substance of good quality even if the level of the side product is as high as 5%. Carryover of impurities is extremely important (see below), purification – not necessarily. It is the good, valid process that makes high quality APIs not the number of the purifications.



ISSUE 4: ISOLATED AND PURIFIED

No comments. We agree to any word in this paragraph.

ISSUE 5: CARRYOVER OF IMPURITIES

No comments. We agree to any word in this paragraph. This is the real justification for the starting material and the relation between its quality and the drug substance quality.

ISSUE 6: COMPLEXITY OF STRUCTURE

The requirement of having the starting material distinguishable from potential isomers (lines 1801-1805) is correct. We, as drug substance manufacturers always invest lots of R&D work to define and identify these isomers and to develop suitable, **valid** analytical methods to detect these isomers in the intermediates as well as the drug substance. However, the declaration in lines 1805-1807 is not connected with the preceding paragraph. Using complex starting materials may require better characterization of this material. It may lead to a good drug substance or low quality drug substance. Good chemistry, good process and high GMP and compliance levels will ensure high quality drug substances, not the complexity of the starting material. The limit set for the complexity of the analytical instrumentation is also not understood. If a company can use highly sophisticated instruments for setting the quality of its starting materials, let it be so. The real issues are whether the methods are valid (and validated), whether the results are meaningful, whether the instruments are properly calibrated and maintained etc. The guidelines for such compliance are there and this is what counts.

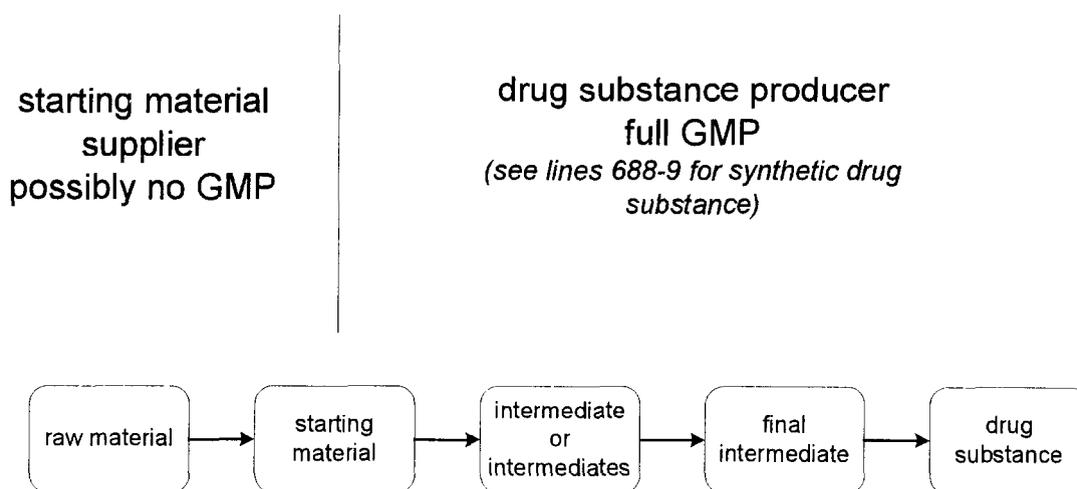
ISSUE 7: POST APPROVAL CHANGES

Regretfully, I cannot follow the logic behind this section (lines 1976-1979). On the one hand the agency requires huge quantities of evidence in order to approve a starting material. On the other hand, once this approval was obtained, there is no control anymore. The drug substance manufacturer can change its starting material suppliers at will, without being committed to serious evaluation of the meaning of this supplier change. It is naivety at its best to assume that the drug substance manufacturer knows everything about the process. This is especially correct regarding analytical specifications. New process for the starting material means possible inadequacy of the analytical methods presently used. The European Pharmacopoeia introduced the term "Certificate of Suitability" for drug substances in order to solve exactly this problem (but for APIs). An API can comply with the EP monograph but still be of unacceptable quality. We feel that on one hand, in the approval stage, the agency is too strict in its requirements while, on the other hand, it is too lenient in the post approval stage.



In the rest of this document we would like to present an analysis of the situation as described in the draft guideline and an alternative situation we propose to evaluate/adopt.

According to the draft guideline the world of drug substance production is divided to two domains. Once a starting material is defined, one domain is the area where the starting material is made and the other domain is where this starting material is converted by a series of chemical processes to the drug substance. This situation is graphically described in the attached scheme.



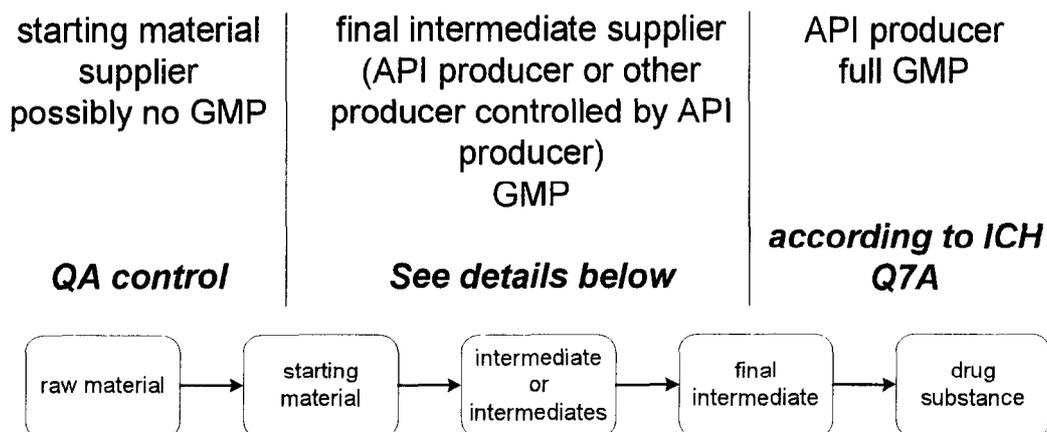
The problem in this approach is that it totally relies upon the quality of a "simple" starting material (having a significant non pharmaceutical market). The model assumes that the producer of the starting material is well aware of what he is doing. Keeping in mind that in many instances this is not the case, the quality (and more important the stable quality) of the product is far from being secured. The model further assumes that executing long sequence (at least 3) chemical steps at the API producer plant guarantees the quality of the drug substance. Regrettably, there is no such guarantee.

The assured quality of the drug substance is the most important issue of the API manufacturer. The concern of the agency is well understood by the industry. The model suggested in the draft guideline is not valid though.

The name of the game is compliance with GMP, materials control, process control and consistent quality. Where a chemical entity is produced is less significant (unless this is a drug substance). At the end of the day, the responsibility for the drug substance is on the API producer. We believe that the quality of the starting material used by the API manufacturer (whether the definition of the starting material is as defined by the draft guideline, or whether it is something else) is a critical factor for obtaining high quality product. But this high quality will be obtained if the API producer is allowed to work hand in hand with an intermediates producer (not necessarily separated from the final intermediate by several reaction steps – it might be even the final intermediate producer himself!). Correct choice of such intermediates producer, coupled with a control and responsibility of the API producer



on what happens in the intermediates producer premises, are the key factor for high quality approvable product.



According to this model it is not crucial where the intermediates are made. They can be prepared at the API manufacturer premises or at other company having GMP and the operations are controlled and oversights by the drug substance maker. There is no doubt that the drug substance producer is responsible for the operations made during the conversion of the starting material to the final intermediate.

At the end we would like to present our vision regarding the relations between the drug substance manufacturer and the intermediate maker and the documentation level needed to be kept in house related to the intermediate maker premises.

REQUIREMENTS FROM THE INTERMEDIATE MANUFACTURER

1. Full control on the production process, testing procedures and monitoring of potential impurities.
2. Full documentation of work according to batch cards including full analytical files relating to these batch cards.
3. Cleaning of multi purpose equipment with a predefined process that meets agreed validation requirements.
4. Calibration of all laboratory equipment and production devices.
5. Suitable maintenance for all production equipment.
6. Use of analytical methods validated to agreed requirements.
7. Established criteria for the education and experience needed for the production and laboratory staff and full responsibility to train and qualify them accordingly.



8. Established full control over all raw materials.
9. Full openness to API manufacturer audits and full transparency towards him in all processes.
10. Strong commitment to get pre-approval from the API manufacturer for all planned changes in the synthetic pathways, reagents, solvents or catalysts used in the manufacturing process, specification, impurity profile, manufacturing site, scale or any other change that might have an effect on the quality of the product. The judgment on the criteria of the implement changes and the reports contents would be done according BACPAC 1.
11. Performance of full failure investigations.
12. Full documentation back up, from raw materials for every final intermediate (FI) that is supplied to the API manufacturer i.e.: detailed flow chart of synthetic route from raw materials to the FI, including all substrates, reagents, catalysts and solvents and indicate whether or not the material is isolated and purified accompanied by a TSE declaration for all raw materials. No specification for the raw material.

This package should be kept at the API plant available for FDA inspection

SUMMARY:

Propinquity and complexity of structure issues (of the starting materials and intermediates) do not warrant the high consistent quality of the API. Process control and material control (as manifested in the carry over of the impurities) and manufacturing control (as shown in our document) are the key factor for getting consistently raw materials needed for producing high quality APIs under GMP and according to the regulations. This document suggests a good way how to have this control and GMP.