

SIO

Global leading manufacturer of
pharmaceutical purified oils.

A subsidiary of ADM



MANAGING THE NATURAL VARIABILITY OF PLANT-BASED PHARMACEUTICAL INGREDIENTS

EXAMPLE OF VEGETABLE OILS

Why managing variability?

Pharmaceutical ingredients play a key role in drug formulation. Variations in their composition and physicochemical properties can have significant impact on the final drug product performances like safety, physical and chemical stability and bioavailability. In the recent past, ingredient variability has been at the origin of FDA recalls.

Natural-based products are by definition subject to a certain degree of variability but appropriate solutions can be developed to manage this variability and propose consistent plant-based pharmaceutical ingredients. As a manufacturer of highly purified vegetable oils, SIO has implemented a full management of this natural variability.

Risk assessment can be used to understand variability of naturally-derived pharmaceutical ingredients and identify which material attributes have an impact on the performances of the final dosage form.



The origins of variability

Natural-based products are by definition subject to a certain degree of variability. It is typically the case of vegetable oils. This variability has different origins like cultivation techniques, weather conditions and soil characteristics. All these parameters play an important role on oil content of the seeds and fruits but also on the fatty acids composition of the vegetable oil.

The supply chain, storage time and condition also impact the quality of vegetable oil. As an example, bad storage conditions can lead to the presence of mycotoxins. Inappropriate drying conditions can lead to the formation of PAH's (polycyclic aromatic hydrocarbons) like benzo(a)pyrene.

The way seeds and fruits are treated for oil recovery is also of prior importance. →

Plant-based products variability



Cultivation techniques

Crop cultivars – Sowing date – Sowing density – Irrigation – Fertilization – Maturity at harvest



Weather conditions

Min/max temperatures – Days of sunshine – Rainfalls/water stress

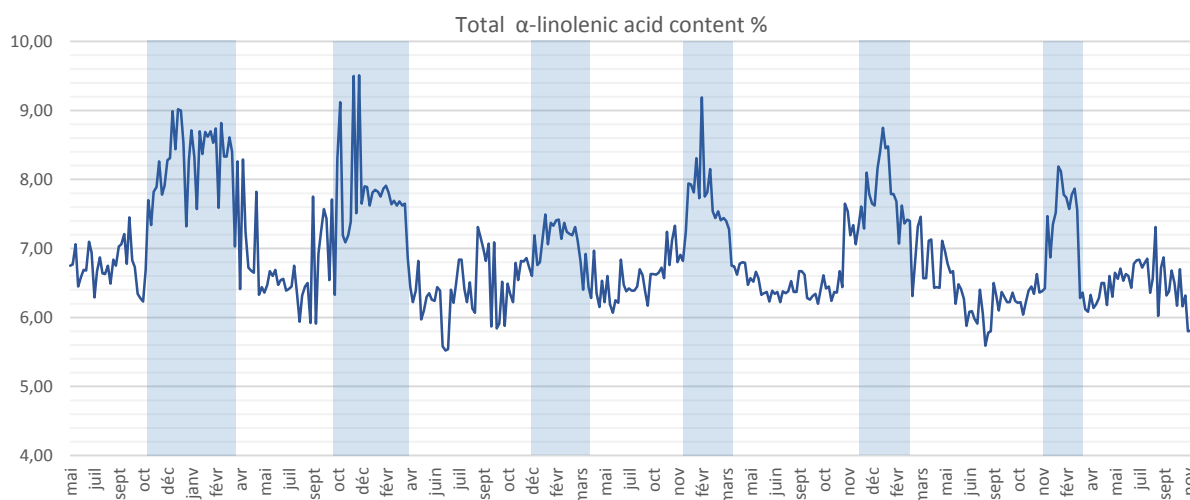


Soil characteristics

Composition – Structure – Soil life

Example of geographic variability of soybean oil (from internal analysis)

As an illustration, this graph shows the variation in α -linolenic acid content of crude soybean oil depending on the geographic origin.



From October to April, soybean oil is sourced from crops grown in the north hemisphere (areas in blue). It gives an oil with a higher content in α -linolenic (average around 7,5%) compared to seeds grown in the south hemisphere with an average content of α -linolenic acid around 6,5%.

Applicable standards

- Nature can provide vegetable oils with a very wide range of characteristics. Available food grade products are regulated by the CODEX ALIMENTARIUS.
- Pharmaceutical ingredients for their part have to comply with pharmaceutical regulatory standards (pharmacopeias) often tighter than food standards.

Besides regulatory requirements, some customers may have very specific needs, often even narrower, related to the formulation of their drug.

The European Pharmacopoeia has introduced in certain excipient monographs a section called "Functionality-Related Characteristics". This non mandatory section explains how functionality should be addressed. The USP General Chapter <1059> on Excipient Performance provides guidance on physical and chemical properties of excipients.

Management of variability

The management of the variability of plant-based pharmaceutical ingredients occurs at each step of the manufacturing process. Several fundamental steps are required: (a) Starting material sourcing, (b) Analytical characterization of its composition (c) Purification process design, (d) Process management and analytical expertise and (e) Stability studies.

(a) Sourcing of the starting material

A major step in managing the variability is the sourcing of starting materials. Indeed, we saw previously that vegetable oils presented different profiles especially due to product variability parameters. It is essential to work closely with starting material suppliers, to discuss and explain clearly what are the needs to guarantee the quality and consistency of the final product.

Following actions are of major importance:

- Selecting a supplier working with a specific crop cultivar and able to mix oils from different origins to guaranty targeted fatty acid profile ; but also with dedicated production lines to avoid cross contamination.
- Working with him to improve his extraction process to avoid oil damage that can lead to purification troubles. As part of the GMP's, suppliers are audited. A pre-delivery sample is sent to the QC lab for analysis and agreement before delivery ;
- Selecting a particular sourcing period over the year to guaranty specific characteristics of the oil like fatty acid composition or specific UV absorbance.

(b) Characterization of the starting material

Crude oil (solvent-extracted like soybean oil) and *virgin oil* (pressure-extracted like olive oil) are used as starting materials for pharmaceutical ingredients. Both sources contain a lot of different compounds.

Some of them are undesirable substances having a negative effect on oil's safety, quality and stability. They need to be removed. Among these are contaminants like pesticides, PAH and heavy metals, free fatty acids, phospholipids, oxidation compounds, flavors, pigments, traces of metal and extraction solvent, microbial contamination, residual solid particles. Each one of those compounds will have an impact on the quality attributes of the product.

Some others are beneficial and need to be preserved as much as possible. That is the case of tocopherols, the natural antioxidants that are naturally present in most vegetable oils. In each case, substances identification need to be done through analytical expertise.

(c) Purification process design

The knowledge of critical product parameters and their link to the corresponding process parameters are key to help minimize fluctuations in pharmaceutical ingredients quality. The purification process needs to reliably and predictably deliver suitable product for human use. Impurities must be removed while an acceptable yield is maintained. At reception, oils are carefully analyzed and only those respecting internal specifications are accepted. Oils are then purified in a 6 steps process including degumming, neutralization, washing, bleaching, deodorization and final filtration up to 0,45 µm. Final packaging is done in ISO 8 classified clean and positive pressure room.

Production is:

- Made by batch for full traceability ;
- Closed to avoid external contamination, under high vacuum to remove residual oxygen and prevent oxidation ;
- Made with nitrogen blanketing to prevent oil oxidation and improve shelf life stability ;
- Organic solvent free ;
- Made with optimized temperature to avoid oil degradation (trans fatty acids formation) and keep natural antioxidants in the oil.

Process is designed to be robust and ensure that the pharmaceutical ingredient will be as constant as possible. Careful analysis of the starting material allows us to adjust our purification process to each batch of starting material, depending on its variability.

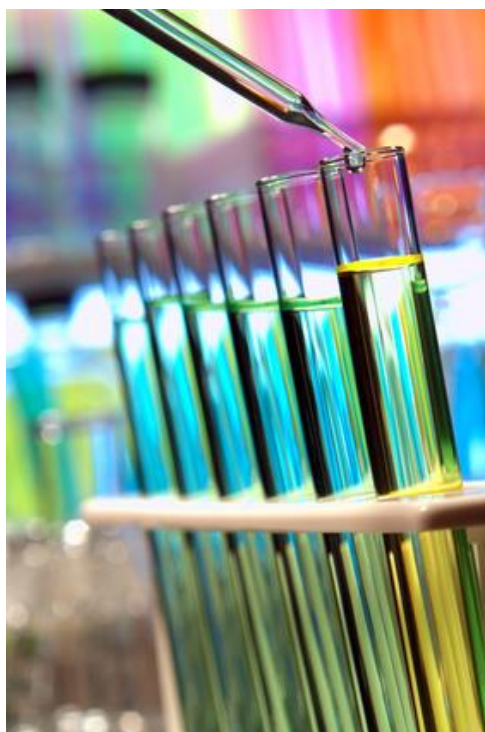
(d) Process management and analytical expertise

Process management is of major importance in managing the variability of naturally derived pharmaceutical ingredients. Analysis of starting material characteristics and real-time process monitoring by the measurement of critical process parameters allow us to fine tune our process conditions to guaranty the best batch to batch consistency.

For excipients as for API's, we carefully manage In-Process Controls (IPC) to ensure that every subsequent batch will comply with internal specifications. As part of process management, Out Of Trends (OOT) is a particular relevant tool to identify immediately any process deviation.

Our company is recognized for its expertise in the analysis of oils and fats. We master the most advanced analytical techniques in compliance with Good Laboratory Practices (GLP), and propose also new and innovative methods to European and US Pharmacopeias, in particular for injectable oils.

In 2014, we have received a certificate from USP recognizing the outstanding contribution of the Analytical Department in the establishment of new monographs for olive and soybean oils. SIO is also involved for over 20 years in the working group of the European Pharmacopoeia in vegetable oils and brings its expertise in developing and improving analytical.



SIO Expertise in oils and fats manufacturing and analysis.

(e) Stability studies

Stability studies are essential to provide evidence of how the quality of an API or excipient varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.

Our API's and excipients are tested according to the International Conference on Harmonization quality guideline ICH Q1A, in storage conditions adapted to the climatic conditions of the country where products are expected to be shipped, as defined by the WHO.

Example of Refined Soybean Oil IV (injectable grade):

Number of batches studies	Study	Storage conditions	Frequency of testing (months)	Study duration time (months)
3	Long term	30°C ± 2°C 65% RH ± 5%	0-3-6-9-12-18-24-36	36
3	Accelerated	40°C ± 2°C 75% RH ± 5%	0-3-6-9-12	12

In this case, storage conditions of Refined Soybean Oil IV have been chosen for tropical zones III and IV.

Stability studies done on our products show that they are perfectly stable over a 36-months shelf life period. Storage and transport conditions are also carefully managed to ensure the best quality of our pharmaceutical ingredients.

Conclusion

Variability of pharmaceutical ingredients should be part of the risk analysis, which is done during the development of the final dosage form. It can be shown to have caused failures and even recalls from health authorities. Naturally derived pharmaceutical ingredients are particularly exposed to this variability. The main challenge for pharmaceutical laboratories is to carefully select suppliers that have the capacity to manage this variability.

SIO manufactures API's and excipients with the same level of requirement. The workshops, manufacturing facilities and analytical equipment are validated and fully qualified. The production complies with cGMP and the facilities are regularly inspected by health authorities such as ANSM and when applicable US FDA.

For us, it does seem normal and essential to have the same strict manufacturing criteria for excipient that represents up to more than 90% of the formula of the drug, than for API itself.



About SIO

SIO is a global leading manufacturer of pharmaceutical grade oils (soybean, olive, sesame) used as API's or excipients for oil-soluble drugs.

As a subsidiary of Archer Daniels Midland Company (ADM) – one of the world's largest agricultural processors and food ingredient providers with 32,300 employees in more than 160 countries – SIO offers an extensive range of highly purified oils, derived from vegetable origins that meet all relevant pharmaceutical regulations and manufactured according to cGMP standards. Thanks to ADM world's premier crop transportation network, we are able to manufacture high quality ingredients for clients anywhere on the globe. Our highly purified pharmaceutical oils are used as API's (CEP for soybean and olive oils) in large volume emulsions for parenteral nutrition and as excipients (soybean US type IV DMF for soybean and sesame oils) in injectable, oral or topical formulations.

In addition, SIO offers contract manufacturing capabilities with cGMP production capacity and labs inspected by the FDA and French authorities (ANSM).

With ADM providing SIO with the best solutions and practices for the sourcing of starting materials used to produce pharmaceutical ingredients, we aim at delivering the best solutions to the very demanding industry of pharmaceuticals.

To find out how we can help you, please contact us:

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