



Precision in Plant-Based Pharmaceutical Ingredients: Managing Natural Variability for Optimal Drug Performance

WHY MANAGING VARIABILITY MATTERS?

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, ADM-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.



With over a century of expertise, ADM provides innovative solutions to the pharmaceutical industry, leveraging dedicated production, specialized R&D, and regulatory teams. Our products comply with major pharmaceutical standards and are produced under strict cGMP guidelines. We prioritize compliance and consistency, enabling innovation with confidence.



THE ROOT OF VARIABILITY

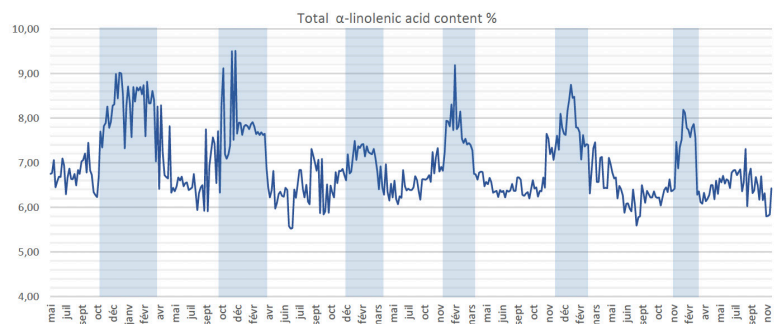
Natural-based products are by definition subject to a certain degree of variability. It is typically the case of vegetable oils. This variability has different origins like cultivation techniques, weather conditions and soil characteristics. All these parameters play an important role on oil content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



EXAMPLE OF GEOGRAPHIC VARIABILITY OF SOYBEAN OIL (FROM INTERNAL ANALYSIS)



As an illustration, this graph shows the variation of α-linolenic acid content of crude soybean oil depending on the months and 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%.

Besides regulatory requirements, customers may require some additional specifications depending on the formulation of their drug.

In the European Pharmacopoeia, the non-mandatory section "Functionality - Related - Characteristics" as part of some monograph explains how functionality should be addressed. The USP General Chapter <1059> on Excipient Performance provides guidance on physical and chemical properties of excipients.

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).



MANAGING VARIABILITY: FROM SOURCING TO STABILITY STUDIES

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 the 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 eliminated impurities, free fatty acids, phospholipids, oxidation compounds, flavors, pigments, residual solvents, and solid particles.

Some others are beneficial and need to be preserved as much as possible. This is the case of natural substances, initially present in the oil, as part of the unsaponifiable matter (e.g. tocopherols) which have interesting properties such as antioxidative properties. These substances are identified through analytical expertise.

(C) PURIFICATION PROCESS DESIGN

The knowledge of critical product process parameters and the process validation 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 maintaining an acceptable yield. At reception, oils are carefully analyzed and only those respecting internal specifications are accepted. Oils are then purified with a chemically refined process, with different monitored steps and a final filtration up to 0.45 µm. Final packaging is done in ISO 8 classified clean and positive pressure room.

Manufacturing process is carried out:

- By batch for full traceability.
- To avoid external contamination, under high vacuum to remove residual oxygen and prevent oxidation.
- Under nitrogen to prevent oil oxidation and improve shelf life.
- Using optimized temperature to avoid oil degradation and preserve natural antioxidants of the oil.

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

(D) PROCESS MANAGEMENT AND ANALYTICAL EXPERTISE

Process control is of major importance in managing the variability of pharmaceutical ingredients of natural origin. Determination of raw material characteristics and real-time process monitoring by measuring critical process parameters allow us to adapt our process conditions to guarantee 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 manage the most advanced analytical techniques in compliance with Good Laboratory Practices (GLP), and propose also new and innovation methods to European and US Pharmacopoeias, 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. ADM-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.





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

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.

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



CONCLUSION

Variability of pharmaceutical ingredients should be part of the risk management 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.

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 ADM

ADM developed a vertically integrated supply chain to ensure reliability & availability of high quality pharmaceutical ingredients. With more than a century of experience, dedicated production lines and specialized R&D and Regulatory teams, ADM-SIO offers its customers innovative global solutions tailored to the specific challenges of the Pharmaceutical industry.

Our extensive range of highly purified oils, derived from vegetable origins, meets major relevant pharmaceutical regulations and are manufactured according to cGMP standards. Using our proprietary technologies, we also have the ability to offer customized solutions to meet your specific needs. We make delivering compliance and consistency a reality, giving you an edge to innovate with confidence.



parenteral
nutrition



injectables



syrup



softgels

Ready to Get Started?

Contact us at
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