Understanding the vitamin supply chain and relative risk of transmission of foreign animal diseases

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Executive summary

- Vitamins are essential nutrients required by swine to optimize health, productivity and well-being
- The U.S. pork industry is dependent on vitamins manufactured in China because there are limited, and in some cases, there are no other country of origin options to meet industry volume demands.
- Initial studies have provided emerging evidence that the African Swine Fever virus (ASFv) can survive in choline chloride, but not vitamin D_3. However, it is unknown if this virus can survive in other vitamins.
- The risk of ASFv or other Foreign Animal Diseases (FAD) being introduced from China into the U.S. through vitamin imports appears to be low, but the impact of introduction is high.
    - Vitamin manufacturing involves many highly technical chemical or fermentation processes that utilize commonly accepted quality control certification schemes and sanitary processes to meet human food grade, and often pharmaceutical standards in the U.S. and E.U. Vitamins imported for use in animal feeds in the U.S. are manufactured in the same facilities and under the same conditions.
    - There is no distinction between human (pharmaceutical) grade vitamin production versus animal feed grade production, unlike some other feed additives and by-products used in the feed industry
    - Although gelatin used in manufacturing vitamin A and D_3 originates from pigskin, there appears to be sufficient thermal treatments used in extracting, concentrating, and sterilizing gelatin to inactivate pathogens.
    - Some vitamin suppliers visit and audit corn cob suppliers for choline chloride production to verify that there is a killing step in corn cob carrier production.
    - Only clean, unused, sealed containers and materials (e.g. pallets) are used for packaging and transporting vitamins to the U.S., usually under hazardous materials shipping standards due to high purity All damaged containers and packages containing vitamins during transport are destroyed and not used in manufacturing swine feeds.
    - Once purified vitamins arrive in the U.S., they are distributed to U.S. vitamin premix manufacturers for blending with carriers. Only carriers produced in North America are used by the U.S. vitamin premix manufacturers to minimize the risk of cross-contamination.
    - Vitamins are produced and transported to the U.S. at the highest purity possible for economic reasons. They are not blended with carriers at the locations of production except for choline chloride. Finely ground corn cobs (60%) are added to some choline chloride products after manufacturing and before transport, and your supplier should give you information about the procurement and processing of this material to assess the impact on disease transmission.
    - The chain of custody from manufacturing to delivery to premix manufacturers is up to 120 days, with an additional up to 90 days holding time until premixes are manufactured, and up to an additional 180 days until vitamin premixes are added to complete swine feeds and delivered to commercial farms. This extremely long holding period from the time vitamins are manufactured in China until they are

consumed by pigs greatly exceeds the required holding time for vitamins of up to 39 days for 99.99% ASFv degradation inactivation that has been suggested based on research to determine half-life of ASFv.
    - The majority of U.S. vitamin importers and premix manufacturers have processes and quality assurance programs in place to prevent the introduction of ASFv into U.S. swine herds.
    - However, there are a few unconventional brokers and traders that may import vitamins from China and market them using limited if any biosecurity and quality assurance control procedures. Obtaining vitamins and premixes from these entities increases the risk of ASFv introduction.
- Pork producers are responsible for selecting reputable suppliers of all feed ingredients by asking appropriate questions to avoid potential suppliers that do not follow standards of feed safety.
- Cross-contamination of vitamin premixes from imported feed ingredients (especially porcine derived) and pet foods could occur in multi-species commercial feed mills if prerequisite or food safety plans are not designed to prevent cross-contamination.
- The evaluation of the effectiveness of using various mitigation procedures such as thermal treatment, irradiation, pH adjustments, and feed additives for feed and feed ingredients contaminated with ASFv is not complete. Most research has focused on the effectiveness of additives added during complete feed processing with other types of viruses which have very different characteristics compared with ASFv. However, vitamins are unique compared to other feed ingredients because they are sensitive to high heat treatment and pH, which can substantially reduce their nutritional value. Therefore, options for treating vitamins and vitamin premixes with these methods is likely not a viable option, and if used, vitamin stability evaluations should be conducted to confirm adequate stability or adjust dietary vitamin concentrations to compensate for potential losses.

Summary of potential risk factors for ASF virus contamination/transmission in the vitamin supply chain

- Purchasing vitamin products from unconventional brokers and traders that do not provide necessary documentation of country of origin, quality assurance, and sanitary transport procedures.
- Cross-contamination of vitamin premixes from imported feed ingredients (especially porcine derived) and pet foods in multi-species commercial feed mills.
- Use of gelatin derived from pigskin when manufacturing vitamin A and D_3.
- Use of ground corn cobs as a carrier during the choline chloride manufacturing process.

Current situation

Extensive interconnectedness of global trade and human mobility has dramatically increased the risk of transmitting foreign animal diseases (FAD) from endemic countries compared with those that do not have these diseases. Several FAD have been identified as potential threats to the U.S. pork industry, especially African Swine Fever (ASFv; Dee et al., 2018).

Feed ingredients contaminated with viruses, which includes some vitamins, have been shown to maintain active virus that could potentially serve as a means of transmission to pigs. Studies have evaluated the survival of Porcine Epidemic Diarrhea Virus (PEDV), Porcine Delta Corona Virus (PDCoV), and Transmissible Gastroenteritis Virus (TGEV) in feed ingredients and showed no differences in survival of PEDV among complete feed, vitamin-trace mineral premix, and other feed ingredients tested (Trudeau et al., 2017). However, PDCoV and TGEV survived longer in soybean meal and corn compared to all other feed ingredients and (Trudeau et al., 2017). In a recent study by Dee et al. (2018), surrogate viruses for Foot and Mouth Disease virus (Seneca Virus A), Swine Vesicular Disease virus (Porcine Sapelovirus), PEDV, and Porcine Circovirus Type 2 virus survived in vitamin D using the length of time in trans-Pacific and trans-Atlantic transport models. Although ASFv did not survive in vitamin D, it did survive in choline chloride along with Seneca Virus A, PEDV, and Porcine Circovirus Type 2. These results have raised questions about the risk of ASF virus survival in other types of imported vitamins. However, it is important to acknowledge that many feed ingredients and pet food products are imported into the U.S. annually. The risk assessment of transmission of ASFv in these feed ingredients and pet food from China has not been determined, but they may pose a greater risk of ASFv and FAD virus transmission than imported vitamins due to less control of cross-contamination from procurement or manufacturing and transit to U.S. destinations (**Table1**).

Table 1. Feed ingredients imported into the United States in 2018 (Source: United States International Trade Commission; https://dataweb.usitc.gov/)

Ingredient	**kg**
Corn grain	794,874,396
Pork and pork derived products	512,302,065
Soybeans	507,524,609
Animal feeds excluding pet food	395,205,327
Dog and cat food	254,881,394
Total vitamin imports for human and animal use	128,453,000

Vitamins represent a significant proportion of total feed ingredient imports (**Table 1**), and some vitamins (biotin, folic acid, pyridoxine, thiamin, and B_{12}) are almost exclusively, or only manufactured in China (**Table 2**), which is endemic with ASFv. Therefore, U.S. pork producers and their feed suppliers have questioned the relative risk of importing vitamins from China for introducing ASFv into North America.

Table 2. Estimates of the quantity and percentage of total vitamins imported into the United States from China in 2018 (Source: United States International Trade Commission; https://dataweb.usitc.gov/)

Vitamin imports (human and animal use)	kg	Estimated % of total vitamin imports
Total	91,534,032	-
Vitamin C	36,435,935	80
Vitamin E and related	27,689,710	55
Niacin (B_3)	9,891,192	50
Pantothenic acid (B_5)	4,781,253	70
Vitamin A	2,257,388	35
Thiamin (B_1)	2,137,934	90
Riboflavin (B_2)	1,507,016	50
Pyridoxine (B_6)	1,367,483	90
Vitamin B_{12}	661,107	90
Folic acid	337,106	40
Other unmixed vitamins and derivatives	4,467,908	70

However, it is important to recognize that 5.1% of imported soybean meal, 11.7% of imported soybeans, and 4.5% of brewery/distillery by-products are imported from ASFv-affected countries (USDA, 2019). These feed ingredients may be a risk factor for the transmission of ASFv and other foreign animal viruses, but there are no published data documenting the presence or prevalence of viruses in imported feed ingredients.

Most vitamin manufacturers produce human and animal grade vitamins using the same quality assurance and controls that meet human grade standards. Third party certification programs (e.g. GMA – **G**rocery **M**anufacturers **A**ssociation; GMP+ - **G**ood **M**anufacturing **P**ractices; FAMI-QS – **F**eed **A**dditive and pre**M**ixture **S**ystem) are used in vitamin manufacturing facilities, which likely minimizes the risk of contamination of vitamin products with ASFv or other viruses (Figure 1). Therefore, the risk of ASFv introduction from vitamins is considered to be low, but if contaminated, vitamins can be a vehicle for virus introduction in the U.S.

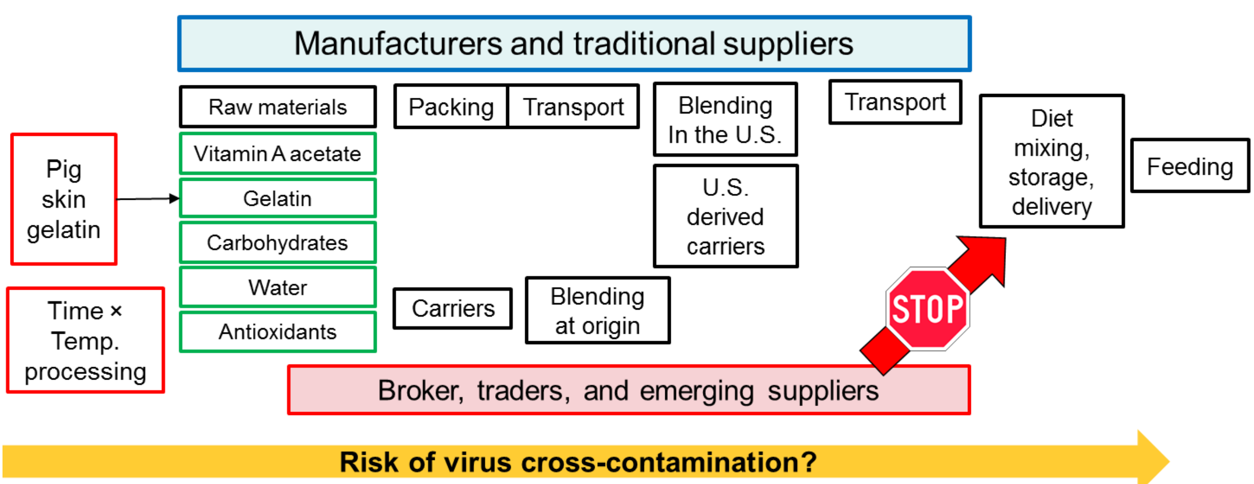

Figure 1. General description of the vitamin supply chain

This means that sanitation practices must be in place after manufacturing and during transport to further minimize the risk of virus contamination. Once these highly concentrated, purified chemical forms of vitamins arrive in the U.S., they are blended with carriers (e.g. rice hulls, corn cobs) to manufacture vitamin or vitamin-trace mineral premixes, which are added at low inclusion rates (1 to 10 lbs/ton) to complete swine feeds. The countries of origin of these carriers are almost exclusively in North America, which pose minimal risk of ASFv contamination because this virus is not present in North America.

It is important to recognize that not all vitamin suppliers follow strict quality assurance and sanitary transport procedures. Unconventional, non-certified, or uninspected vitamin brokers and traders exist in the vitamin supply chain, which may pose a greater risk of ASFv introduction. Therefore, pork producers should be diligent when selecting only vitamin suppliers and choose those that adhere to the highest quality assurance and sanitary transport procedures. In addition, there is potential risk of cross-contamination in multi-species feed mills if other imported feed ingredients from ASFv endemic countries are used in manufacturing complete feeds.

Vitamins are essential nutrients in swine diets

It is well established that vitamins are required nutrients in swine diets to avoid deficiencies and optimize growth, reproduction, health and well-being of pigs (NRC, 2012; Barroeta et al., 2011). Although many commonly used feed ingredients, such as corn, soybean meal, dried distillers grains with solubles, and wheat middlings contain vitamins, the concentrations, potency, and bioavailability are considered inadequate to meet the pig's requirements. Therefore, vitamin requirements are met in commercial swine diets by properly formulating vitamin and vitamin-trace mineral premixes used as supplements in complete feeds. A list of required vitamins supplemented in swine diets is shown in **Table 3**.

Because vitamin supplementation is essential in swine diets, volumes of vitamins imported must match industry needs, and the majority of vitamins used in swine premixes in the U.S. are imported from China, several questions about the potential risk of ASFv transmission at various stages of the vitamin supply chain need to be answered:

1. Where are vitamins manufactured?
2. What are the processes used to manufacture vitamins?
3. What are the quality control and biosecurity procedures used to manufacture vitamins?
4. Are the processes and ingredients used to manufacture vitamins safe?
5. Are the packaging materials safe?
6. What is the typical length of time from vitamin manufacturing in China until vitamins are consumed by pigs on commercial farms in the U.S.?
7. What is the risk of cross-contamination of shipments of purified vitamins in the supply chain?
8. How are vitamin premixes made?
9. Are all vitamin product providers reputable?
10. What is the additional risk of ASFv transmission in multi-species feed mills compared with single species feed mills?

11. Can additional biosecurity and sanitary practices and traceability be implemented in the vitamin supply chain to minimize risk of virus transmission?
12. Are there effective mitigation treatment strategies that can be used to inactivate ASF if it is present?

Table 3. Chemical and commercial synthetic forms of vitamins required by pigs

Vitamin[1]	**Chemical forms[1]**	**Commercial forms of straights[2]**
A	Retinol Retinal Retinoic acid	Vitamin A beadlet – Cross-linked Vitamin A beadlet – Non S. Cong. non-cross-linked
D_3	Cholecalciferol	Vitamin D_3 beadlet (A/D_3) Cross-linked Vitamin D_3 S. Cong. Vitamin D_3 SD Vitamin D_3 drum dried
E	DL-α-tocopheryl acetate D-α-tocopheryl acetate D-α-tocopherol	Vitamin E acetate (50%) Vitamin E alcohol, natural
K (menadione)	2-methyl-1,4-naphthoquinone	Menadione sodium bisulfate (MSB) MSB coated Menadione dimethylpyriminol bisulfite (MPB) Menadione sodium bisulfate complex (MSBC) Menadione nicotinamide bisulfite MNB
Biotin (B_7)	Biotin	Biotin
Choline	Choline chloride	Choline chloride
Folacin (B_9)	Folate Folic acid Pteroylglutaminc acid	Folic acid
Niacin (B_3)	Nicotinic acid Nicotinamide	Niacin Niacinamide
Pantothenic acid (B_5)	D-calcium pantothenate DL-calcium pantothenate-calcium chloride complex	Calcium pantothenate
Riboflavin (B_2)	Riboflavin	Riboflavin
Thiamin (B_1)	Thiamine	Thiamine HCl Thiamine Mono
Pyridoxine (B_6)	Pyridoxine Pyridoxal Pyridoxamine	Pyridoxine
Cyanocobalamin (B_{12})	Cyanocobalamin	Cyanocobalamin

[1]Information from NRC (2012)

[2]Information adapted from BASF, Animal Nutrition, 6th edition (2000) and DSM, Optimum Vitamin Nutrition for Pigs, 12th edition (2016)

Where are vitamins manufactured?

The majority of global vitamin production at needed volumes occurs in China. Given the magnitude of the ASFv epidemic in China, feed ingredients produced in China, including vitamins, have become a target for questioning their contribution to the potential risk of transmission of FADs including ASFv. **Table 4** provides estimates of the total production of various vitamins produced in China. Note that with the exception of vitamin A, E, and niacin, 80 to 100% of all other vitamins must be imported from China. For biotin, folic acid and vitamin B_{12}, there are no other sources beyond China to acquire these vitamins. Therefore, there are limited options for sourcing most vitamins from countries or regions outside of China in the market today. In fact, compared with a previous survey of vitamin manufacturing companies and locations in China (Enting et al., 2010), it appears that the contributions of Chinese manufacturers to total global vitamin production has increased during the last 9 years. See **Appendix 1** for a listing of the major vitamin manufacturers, vitamin products, and manufacturing location.

Table 4. Current estimates of the percentage of global vitamin production from China compared with other countries and regions (data obtained from vitamin industry sources).

Vitamin	China, %	European Union, %	India, %	Korea, %	Uruguay, %
A	35	65	-	-	-
D_3	80	10	10	-	-
E	58	42	-	-	-
K (MNB)	78	10	-	-	12
Thiamine (B_1)	90	10	-	-	-
Riboflavin (B_2)	50	25	-	25	-
Niacin (B_3)	37	43	20	-	-
Calcium pantothenate (B_5)	80	20	-	-	-
Pyridoxine (B_6)	90	10	-	-	-
Biotin (B_7)	100	-	-	-	-
Folic acid (B_9)	100	-	-	-	-
B_{12}	100	-	-	-	-
Vitamin C	85		-	-	-

What are the processes used to manufacture vitamins?

Vitamins are manufactured using proprietary chemical or fermentation processes that involve time, temperature, and pH conditions that are likely to inactivate viruses if they are present. Vitamin manufacturing is a highly technical, hygienic process suitable for achieving pharmaceutical grade products meeting current human health and safety standards (see **Appendix 2** for photos of vitamin production facilities in China). In fact, there is no distinction between human (pharmaceutical) grade vitamin production versus animal feed grade production, unlike some other feed additives and by-products used in the feed industry. Purified forms of vitamins are called “straights”, which is the form imported into the U.S. without blending with premix carriers, except for choline chloride that is imported blended with corn cobs or other carriers.

For fat-soluble vitamins (A, D_3, and E), examples of manufacturing processes are shown in **Figures A3.1, A3.2, A3.3, and A3.4 in Appendix 3**. Examples of raw materials used in manufacturing these vitamins and the origin is shown in **Table 5**, and the temperature and duration of heating processes for vitamins A, D_3, and E are shown in **Appendix 4**. The manufacturing process for these vitamins generally involves adding ingredients at various stages, dissolution and emulsification, spray granulation, drying, heating, drying, mixing, and sieving. Therefore, there is some thermal exposure during the production process that may be adequate to inactivate any virus if it is present. However, the necessary time and temperature of exposure to inactivate ASFv in vitamins has not yet been determined.

The water-soluble vitamins (B vitamins) are produced using various proprietary fermentation and chemical processes. Examples of processes used to produce riboflavin, calcium pantothenic acid, and choline chloride are shown in **Figures A3.5, A3.6, and A3.7, respectively in Appendix 3**. Additional descriptions of main ingredients and general production processes for various forms of vitamin K and other B vitamins are shown in **Table A3.1 of Appendix 3**. The temperature and duration of heating processes for biotin is shown in **Appendix 4.**

Table 5. Examples of composition and origin of raw materials used to manufacture selected vitamin products produced by Zhejiang Medicine Co., Ltd. in China

Vitamin product	Composition	Manufacturing location
Vitamin A 650, feed grade	Vitamin A acetate	Shaoxing, Zhejiang Province
	Gelatin	Wenzhou, Zhejiang Province Xiangyin, Hunan Province
	Corn starch	Haiyan, Jiaxing Province
	Glucose	Hohhot, Inner Mongolia
	Ethoxyquin/BHT	Yixing, Jiangshu Province Nanjing, Jiangshu Province
	Silicon dioxide	Taiwan
Vitamin A 1000, feed grade	Vitamin A acetate	Shaoxing, Zhejiang Province
	Gelatin	Wenzhou, Zhejiang Province Xiangyin, Hunan Province
	Corn starch	Haiyan, Jiaxing Province
	Glucose	Hohhot, Inner Mongolia
	Ethoxyquin/BHT	Yixing, Jiangshu Province Nanjing, Jiangshu Province
	Silicon dioxide	Taiwan
Vitamin D_3 500, feed grade	Vitamin D_3 oil (Cholecalciferol)	Shaoxing, Zhejiang Province
	Gelatin	Wenzhou, Zhejiang Province Xiangyin, Hunan Province
	Corn starch	Haiyan, Jiaxing Province
	Sugar	Liuzhou, Guangxi Province
	BHT	Yixing, Jiangshu Province Nanjing, Jiangshu Province
	Silicon dioxide	Taiwan
Vitamin E – all-rac-alpha-tocopheryl acetate 50% feed grade	Vitamin E acetate	Shaoxing, Zhejiang Province
	Silicon dioxide	Wuxi, Jiangshu Province Qihe, Shangdong Province

Although vitamin manufacturing facilities are located in Chinese provinces that are endemic with ASFv, they are gated with strict security and biosecurity procedures in place to prevent unwanted visitors, pests, rodents, and animals from entering the premises (**see Appendix 2 for photos of**

actual facilities). However, specific details of biosecurity practices and third-party audits are unclear at this time.

What are the quality control and biosecurity procedures used to manufacture vitamins?

Many Chinese vitamin manufacturers indicate using various Quality Assurance certification schemes such as ISO, HACCP, GMP+, FAMI-QS, Kosher, HALAL, and others (Enting et al., 2010). Most feed safety and quality certifications were developed to ensure practices that prevent contamination and minimize risks. However, specific considerations for ASFv and other FADs have not been a primary focus when considering virus contamination as a potential hazard. Therefore, the existing feed safety and biosecurity protocols may need to be improved in the future, with greater consideration for implementing practices that further minimize the risks of contamination with important viruses.

With the exception of GMP+ and HACCP, implementation and compliance with these certification programs is voluntary in most countries. In other words, most certification programs are implemented based on requirements of customers and are not official regulations. Therefore, the types and use of quality assurance programs vary among Chinese vitamin manufacturers because the Chinese government considers them to be voluntary. As a result, some companies may claim that they are compliant with certifications for marketing purposes, but do not put much serious effort into actual implementation or compliance (Enting et al., 2010). However, leading vitamin manufacturing companies have implemented extensive quality assurance and quality control programs because they must comply with strict quality assurance requirements from their export customers in the European Union and the United States. In fact, all reputable vitamin manufacturers and suppliers to the U.S. feed industry can provide detailed information upon customer requests regarding the GMP, ISO 9001, ISO 22000, and HACCP procedures and compliance with FSMA. A summary of certification schemes used by many of the major vitamin manufacturers is provided in **Appendix 5**. In addition, several Chinese vitamin manufacturing companies provide information and documentation of various quality assurance certifications on their web sites (**see Appendix 1**). Reputable vitamin manufacturers and premix suppliers are capable of providing the following types of statements to customers upon request:

- Statements verifying the year and type of quality certifications
- Statements of composition, country of origin, and manufacturing location of vitamins
- Statements of source and country of origin of gelatin used in manufacturing vitamins A and D_3
- Vitamin product African Swine Fever virus biosecurity safety statements
- Statements of composition, country of origin, and manufacturing location of vitamin premix carriers, diluents, and dust suppression agents
- Statements of non-use of porcine-derived ingredients used to manufacture premixes
- Documents of current Good Manufacturing Practices (GMP's) and Frequently Asked Questions for customers

For example, descriptions of GMP's often include detailed descriptions of the following:

- General company information
- Quality management processes including internal and external third-party audits

- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Material management
- Production preventative controls and hazard analysis
- Packaging and labeling
- Storage and distribution
- Laboratory controls
- Validation and qualification
- Rejection and reuse of material
- Sanitary transport standards
- Foreign supplier verification
- Supply chain controls
- Complaints and recalls
- Social responsibility

It is important to know that there are distinct differences among various quality certification schemes. The FSMA program is a regulatory requirement for pet food and feed manufacturers and importers, which includes GMPs and a food safety plan, but does not include virus monitoring or controls. Use of voluntary quality assurance programs (e.g. ISO, GFSI, GMP+, etc.) depends on customer requirements, but also do not include virus monitoring and control.

Biosecurity programs have been implemented in several vitamin manufacturing companies in China, which are focused on further reducing the risk of ASFv exposure. These programs do undergo a third-party audit to verify compliance (**see Appendix 6**). If these requirements are not met, partnerships with U.S. vitamin and feed companies are terminated. Although these biosecurity programs are in place, they are not standardized across the entire vitamin manufacturing industry and may require further development.

The biosecurity requirements that have been implemented are as follows:

1. All laws and regulations to prevent the spread of infectious diseases, such as ASFv, must be followed.
2. Confirm that your employees do not work on a farm, or own, breed, or have contact with swine.
3. Do not house or breed any animal in your facility or facility grounds.
4. Implement and enhanced pest control program in your facility and facility grounds.
5. Work clothes cannot come in contact with any swine, raw pork or pork products, which includes employee meals.
6. Establish disinfection points for people and vehicles at entrances of the site, buildings manufacturing your products, and storage facilities, especially for vehicles to and from premix operations. Personnel and visitors entering the facilities should ensure that shoes, clothing, and equipment are disinfected. Employees cannot take work shoes, clothing, and equipment to home or out of facilities.

7. Disinfect pallets and containers used for end products before shipping (such as heat-treated pallets or chemical treatments).
8. Anyone coming from ASFv infected areas is not allowed to visit the facility.
9. Any vehicle coming from and ASFv infected area is not allowed to enter the facility or facility grounds.
10. Disinfection methods and the concentration of disinfectant used must be documented and verified. The ASFv can be inactivated by 8/1000 sodium hydroxide (30 minutes), hypochlorites – 2.3% chlorine (30 minutes), 3/1000 formalin (30 minutes), Consult your epidemic prevention departments to learn more about disinfectants.

For detailed information on the certification criteria for the various quality assurance schemes, as well as guidelines for biosecurity, foreign supplier verification, and good manufacturing procedures are available by accessing the following links:

FAMI-Q:
https://www.fami-qs.org/home.html

FSMA – Food Safety Modernization Act
https://www.fda.gov/food/guidance-regulation-food-and-dietary-supplements/food-safety-modernization-act-fsma

GMP+
https://www.gmpplus.org/en

HACCP – Hazard Analysis and Critical Control Points
https://www.fda.gov/food/hazard-analysis-critical-control-point-haccp/haccp-principles-application-guidelines

ISO – International Organization for Standardization
https://www.iso.org/certification.html
https://www.iso.org/iso-9001-quality-management.html

Global Food Safety Initiative
https://www.mygfsi.com/

Biosecurity Guidelines from AFIA
https://www.afia.org/pub/?id=E348BF9F-98ED-09DB-A45D-504737FE7AE2

Guidelines for Foreign Supplier Verification Program
https://www.fda.gov/food/food-safety-modernization-act-fsma/fsma-final-rule-foreign-supplier-verification-programs-fsvp-importers-food-humans-and-animals

Good Manufacturing Procedures Guidelines from FSMA
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-235-current-good-manufacturing-practice-requirements-food-animals

Are the processes and ingredients used to manufacture vitamins safe?

The time, temperature, and pH conditions used during the vitamin manufacturing process may be adequate to inactivate ASFv and other viruses if they are present. However, a detailed risk assessment of these conditions has not been conducted due to lack of specific process data and uncertainty of the conditions necessary to inactivate the ASF virus. Although the manufacturing processes of each type of vitamin are unique and proprietary, there are several common attributes:

1. There is no separate manufacturing process for human food grade and animal feed grade vitamin manufacturing. All processes used in these "pharmaceutical grade" facilities adhere to strict hygiene and sanitation standards. The same equipment, processes and procedures are used to produce both human food grade and animal feed grade vitamins.

2. All vitamin manufacturing facilities have various quality control and quality assurance certification schemes in place. Although many of the manufacturing facilities supplying vitamins to the U.S. comply with these standards through third party audits, it is uncertain if all Chinese manufacturing facilities are in compliance.

Gelatin derived from pigskin is used to coat vitamin A and D_3 to preserve potency and biological activity during transport and storage before being added to complete feeds. Although gelatin derived from pigskin may be a source of viruses in these vitamins, manufacturers use multiple thermal treatments during multiple extraction and sterilization processes that are likely to inactivate viruses if they are present. Although the general thermal processing conditions are similar among gelatin manufacturers (**Figure 2**), they may vary somewhat from one manufacturer to another. The following are two examples of current processes described by vitamin manufacturers:

1. Raw material (pigskin) may be obtained from countries that are either endemic with ASFv (i.e. China), or countries of origin that are ASFv-free, depending on the vitamin manufacturing company. Pigskin is processed $\geq$ 60°C for $\geq$ 6 hours followed by UHT sterilization at 138°C for $\geq$ 4 seconds and dried at 28 to 55°C.

2. Pigskin gelatin is prepared at pH < 3 for at least 5 hours. After rinsing, it is placed in hot water at $\geq$ 50°C to extract gelatin broth for $\geq$ 3 hours. During the evaporation process, the gelatin broth is processed at a temperature of 55 to 98°C followed by a double heat treatment of $\geq$ 115°C for $\geq$ 4 seconds.

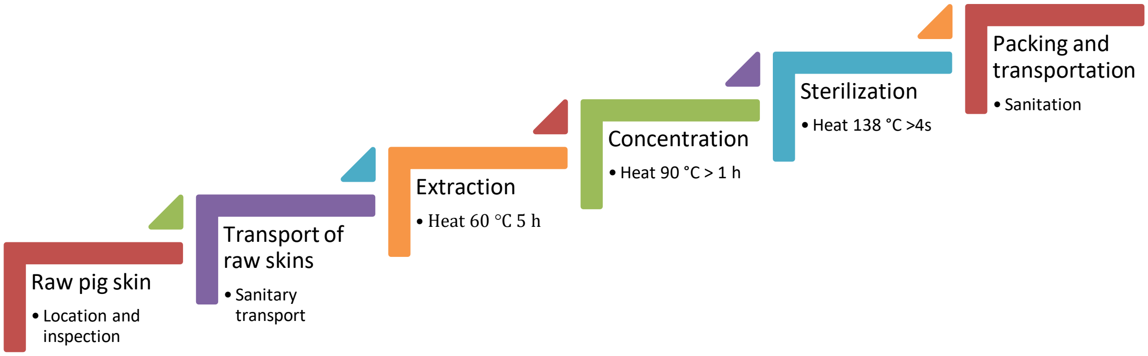

Figure 2. Overview of gelatin manufacturing processes.

Most vitamin A and D_3 manufacturers in China do not offer gelatin-free products, but two manufacturers have the capability of doing this if purchased in large quantities. A few Chinese vitamin A and D manufacturers have considered using bovine-derived gelatin, but have determined it is not as effective as gelatin derived from pigskin, and bovine-derived gelatin is prohibited in most export markets because of potential risk of BSE/TSE.

Choline chloride is often blended with purified, finely ground corn cobs at the country of origin (e.g. China). Some vitamin suppliers visit and audit corn cob suppliers for choline chloride production to verify that there is a killing step in corn cob carrier production, but the origin and specific processes used to produce ground corn cobs as a carrier for choline chloride are unknown at this time, and need to be investigated as a potential risk factor for virus transmission. Although processes may vary among choline chloride manufacturers, corn cobs are commonly mixed with a corn cob carrier before drying, which ranges from 125-138°C for 2 hours to 140-180°C for 2 hours. However, it is important to note that not all choline chloride products in the market use ground corn cobs as a carrier. For example, Animix LLC (Juneau, WI) provides choline chloride using silica as a carrier instead of corn cobs. In addition, liquid forms of choline chloride are also manufactured by a few companies which do not contain a carrier.

Are packaging materials safe?

Most vitamin suppliers pack purified vitamin products in sealed containers, and have extended chain of custody of the products of up to 120 days. The development and implementation of a formal chain of custody exists for most vitamin manufacturers but there may be opportunities for further refinement https://www.foodsafetymagazine.com/magazine-archive1/junejuly-2014/ingredient-chain-of-custody-impact-on-food-safety/. All vitamin products are required to be packaged in new, unused packaging materials including pallets.

What is the typical length of time from vitamin manufacturing in China until vitamins are consumed by pigs on commercial farms?

Once purified vitamins reach a premix blending facility, there are multiple supplier questionnaires that are reviewed and vetted before blending. This is done on a global basis, and any concerns identified during this process will lead to an audit of the source facility. To preserve the nutritional value of vitamins and minimize vitamin potency losses, most vitamin suppliers attempt to minimize holding time before vitamins are fed to pigs. Current holding times (about 90 days) from the time of manufacturing to premix manufacturers, and additional holding times before premixes are incorporated into complete feeds at commercial feed mills (about 6 months), is sufficient to achieve the required holding time (up to 39 days) to inactivate ASF virus based on current research results (SHIC, 2019).

What is the risk of cross-contamination of shipments of purified vitamins in the supply chain?

Purified forms of vitamins are called “straights”, which is the form of all vitamins imported into the U.S. without blending with premix carriers. Vitamins are not premixed during manufacturing or prior to shipment to the U.S. because of the extra cost that would be incurred due to the added weight of premixes compared with purified forms. Therefore, there is almost no blending with carriers or post-processing at the place of origin (e.g. China).

For many U.S. vitamin suppliers, transportation of vitamins from the factory to distribution center is monitored and regulated. All vehicles are required to be clean, dry, and have non-contaminated equipment. Trailers are closed and protected from rain and dust. No co-loading with other chemicals, pharmaceuticals, meat products or any other goods that could be a potential source of contamination is allowed. Any equipment or trailers used to transport live or dead animals is strictly prohibited, and no animal contact inside or outside of transport vehicles is allowed. All ocean carriers are required to provide clean and undamaged containers. Shipments to the European Union are required to be cleaned and disinfected according to EU law, and carriers must comply with EU regulations (DSM, 2019).

Any damaged bags that may occur from the time of initial packaging until arriving at a U.S. destination are discarded, despite economic loss, and are not re-packed or subsequently used due to liability of loss of potency or cross-contamination with other materials.

Once purified vitamins arrive in the U.S., the containers or packages are stored in warehouses at temperatures of 50 to 60°F. All bags and containers come with a certificate of analysis (or certificate of conformance) indicating when it was manufactured for every lot (batch) of every vitamin. If it is a customer requirement, customized documentation with additional information can be created and provided, but may add additional cost that would be incurred by customers (pork producers).

How are vitamin premixes made?

Supplemental vitamins are required in very small quantities in complete swine diets. To provide convenience and ensure homogenous distribution of vitamins in complete feeds, vitamin or vitamin-trace mineral premixes are formulated and mixed as separate ingredients to add to complete diets. Premixes are manufactured by using carriers or diluents and flow agents to dilute the concentration of vitamins while achieving desired concentrations in complete feed after they are added to the diet. All carriers and diluents used in manufacturing swine vitamin premixes in the U.S. are obtained from sources in North America.

The chemical and physical characteristics of straight vitamins vary substantially, which affects the rate of potency or bioavailability losses during storage before use. Therefore, selection of carriers based on their ability to adsorb (moisture attachment to surface of solids) and absorb (moisture movement into pores and crevices of solids) which causes losses in vitamin potency and bioavailability (BASF, 2000). Carriers are chosen based on their adsorption and absorption capability and cost (**Table 6**). High absorption carriers are not recommended for dry vitamins because they significantly reduce bioavailability (BASF, 2000). Therefore, high and medium adsorption carriers (ground corn cobs, rice hulls, and silica) are commonly used for choline chloride and vitamin E straights to maintain high bioavailability (BASF, 2000). Mineral oil is also commonly added to premixes to reduce dust and improve flowability.

Table 6. Relative absorption and adsorption properties of commonly used carriers in vitamin premixes (adapted from BASF, 2000)

Absorption and adsorption capability	Carrier
High absorption	Verxite/vermiculite, zeolite
Low absorption	Silica
High adsorption	Wheat midds, corn cob meal, silica
Medium adsorption	Rice hulls
Low adsorption	Limestone

Carriers are used to maintain a homogenous distribution of vitamins in a premix by minimizing segregation during transportation and storage over time. In addition to the types of carriers shown in **Table 6**, wheat bran, ground almond hulls, and soybean meal have been used in manufacturing vitamin premixes (BASF, 2000). Several chemical and physical characteristics of carriers are important for vitamin premixes including particle size (flowability); bulk density (manufacturing throughput and stacking of pallets); low moisture (< 5% to prevent loss of vitamin potency); non-hygroscopic (minimal ability to attract moisture); low lipid content (< 4% to prevent loss of fat-soluble vitamin potency); non-electrostatic; pH (vitamin stability); and dust (**Table 7 and 8**; BASF, 2000; 2018). It is unknown whether any of these physical and chemical characteristics may affect ASFv survival if premixes are contaminated. In addition, it is unknown if the physical and chemical properties of vitamins affect ASFv survival, but a summary of some of these characteristics is provided in **Table 9**.

Table 7. Selected physical and chemical properties of carriers used in vitamin premixes (BASF, 2000)

Carrier	Moisture, %	Dust, %	Hygroscopicity (7 days – water absorption), %	Adsorbing capacity	pH
Ground rice hulls	5.0	0.09	2.25	Medium	6.3
Fine ground limestone	0.2	0.09	0.02	Low	9.2
Coarse ground limestone	0.4	0.04	0.44	Low	9.0
Dried wheat midds	5.0	0.03	11.7	High	6.9
Ground corn cobs	5.0	0.03	8.13	High	5.4
Dicalcium phosphate	2.8	0.09	6.20	-	3.4
Calcium propionate	1.3	1.09	1.66	-	6.7

Vermiculite	5.1	0.04	3.37	Very High	6.3
Silicon dioxide	4.4	1.04	5.75	Very High	6.9

Table 8. Relative ranking of various carriers used in vitamin premixes based on physical and chemical characteristics, impact on vitamin bioavailability, and price (adapted from BASF, 2018)

Carrier	Lipid, %	Bulk density, lbs/cu. ft. (loose)	Impact on vitamin bioavailability	Price	Overall rank (1 = excellent, 10 = poor)
Dried wheat midds	3.6	22	None	Medium	3
Fine ground limestone	0	62	None	Low	7
Ground rice hulls	0.5	19	None	Low	2
Ground corn cobs	0.4	26	None	Low	2
Novasil^{TM*}	0	34	None	Medium	4
Silicon dioxide	0	14	None	Very High	2
Vermiculite	0	8	Very High	Medium	10

*Novasil Anticaking Agent BASF Co. Floham Park, NJ.

Table 9. Selected physical and chemical properties of vitamins (BASF, 2000)

Vitamin	Moisture, %	Dust, %	Humidity absorption (7 days), %	pH
Vitamin A beadlet	4.1	0.05	9.11	5.7
Vitamin D_3 500	3.4	0.05	13.35	6.4
Vitamin E 50% SD	1.3	0.13	8.80	6.8
Vitamin E 50% ADS	1.3	0.53	1.77	7.1
MSBC	ND	ND	ND	7.0
MPB	ND	ND	ND	4.0
Biotin 2% SD	7.1	0.53	5.07	4.0
Calcium-d-28 pantothenate	0.41	10-15	8.07	6.8-8.0
Calcium-dl-30 pantothenate	0.41	10-15	15.19	6.8-8.0
Thiamin monohydrate	4.2	0.15	0.40	7.0
Thiamin HCl	4.2	0.15	0.55	3.0
Nicotinic acid	0.08	0.09	0.03	3.4
Niacinamide	0.21	0.07	5.50	6.0
Riboflavin 96% crystalline	0.41	0.15	0.13	5.5
Riboflavin 80% SD	1.34	0.02	3.39	5.6

Are all vitamin product providers reputable?

No. As for almost every feed ingredient in the global market, brokers and traders exist in the vitamin market and may not adhere to strict sanitary standards or purchase vitamins from manufacturers that do not comply with quality assurance standards. As a result, it is essential that vitamin premix purchasers request documentation of compliance with quality assurance certification and Good Manufacturing Practices. Reputable and reliable vitamin and vitamin premix providers will provide this type of documentation upon request.

What is the additional risk of ASFv transmission in multi-species feed mills compared with single species feed mills?

Previous studies have shown that Porcine Epidemic Diarrhea Virus survives in various feed ingredients and can serve as a source of cross-contamination in feed mills (Schumacher et al., 2017; Huss et al., 2017; Gebhardt et al., 2018; Schumacher et al., 2018). Unfortunately, no studies have been conducted to determine the potential risk of cross-contamination of ASFv in multi-species feed mills if it is present in other imported feed ingredients (e.g. porcine derived feed ingredients) from ASFv endemic countries, and these ingredients are used in manufacturing complete feeds. Pork producers should request country of origin information of all feed ingredients used from their commercial feed mill supplier, especially if manufacturing feeds for multiple species.

Can additional biosecurity and sanitary practices and traceability be implemented in the vitamin supply chain to minimize risk of virus transmission?

A comprehensive risk assessment has not been conducted to identify potential risks of ASFv transmission in existing quality control certification programs. Current quality assurance certification schemes do not specifically address prevention or control of viral pathogens in feed ingredients, but often address bacterial contamination and are general risk assessments of potential non-microbiological hazards. However, some certification programs apply HACCP principles to minimize potential risk of acquiring pathogens from their origin. Therefore, if necessary, vitamin manufacturers and other segments of the vitamin supply chain could adjust their biosecurity and quality assurance programs to prevent known risks of viruses from entering the supply chain as needed. Perhaps the most practical and efficient way to do this is would be to develop a biosecurity module that can be added to existing quality assurance certification programs during time periods deemed as “high risk” for viral contamination, when extra monitoring and controls are needed, and then removed once the risk is no longer a potential concern.

Guidelines for developing a risk-based plan to mitigate virus transmission from imported feed ingredients has been developed (Schettino et al., 2019). This framework involves applying pre-requisite programs of raw material controls, production controls, sanitation and maintenance, pest control, and sanitary product transport. These programs can be applied at different steps in the supply chain including manufacturing, sanitation, and transport, which are based on the principles of the Food Safety Modernization Act to prevent or reduce the risk of hazards being present in the final product.

In the future, the use of blockchain technology can provide tremendous benefits and efficiencies for improving feed safety and animal health (Zhang et al., 2019). However, several significant limitations must be overcome to realize its benefits which include: 1) tracking of bulk commodities versus packaged feed products such as vitamins; 2) complete and honest participation of all segments of the supply chain; 3) development of methods and standards including third-party verification and data sharing protocols; and 4) overcoming lack of economic incentives to attract participants (Zhang et al., 2019).

Successful implementation of blockchain technology in the vitamin supply chain may be possible because of the relatively limited number of manufacturing companies, importers, and premix manufacturers compared with commodity-based segments of the feed industry, which may facilitate complete participation and coordination. Secondly, purified vitamin products and vitamin premixes are packaged with data indicating date of manufacture, lot or batch number, company, and location. Third, vitamin manufacturers have extensive internal data on quality assurance procedures and certification because record keeping and data collection are required as part of these processes. Finally, there may be economic incentives to implement blockchain in the vitamin supply chain to minimize liability risk of recalls because many of these products are also used as human supplements and food products.

Are there effective mitigation treatment strategies that can be used to inactivate ASF in vitamin premixes if it is present?

Unlike other nutrients, vitamins are sensitive to moisture, hygroscopicity (ability to attract moisture), pressure (heat), heat, friction (heat), oxidation, trace minerals (oxidation), pH, and interactions with other ingredients (BASF, 2018; DSM, 2016). Therefore, use of mitigation strategies that have been shown to be effective for PEDv, such as additives, pH, and thermal treatment will likely reduce vitamin bioavailability to varying amounts, even if they are effective in inactivating ASFv.

Unfortunately, unlike PEDv, very little is known about the conditions necessary to inactivate ASFv if it is present in feed or feed ingredients. African Swine Fever virus is highly resistant to low temperatures but can be inactivated by heat at 56°C for 70 minutes and 60°C for 20 minutes (OIE, 2009). However, the extent of post-manufacturing thermal treatment of purified vitamins and premixes can cause significant losses in bioavailability and nutritional value. For example, using a minimal pelleting temperature of 66 to 70°C can result in losses in vitamin potency of 1 to 35% (65-99% stability; **Table 10**; BASF, 2018). If greater pelleting temperature is used (106 to 110°C) is used, losses in vitamin potency are further reduced (5 to 77%; **Table 10**; BASF, 2018). Similarly, extrusion involves use of high temperatures (91 to 145°C), and is considered to have the greatest effect on reducing vitamin activity when combined with pressure, moisture, and redox reactions during the process (BASF, 2018). Vitamin losses from extrusion can range from 6 to 95% (5-94% stability; **Table 10**; BASF, 2018). Additionally for some vitamins, losses are increased when they are combined with trace minerals in concentrated premixes because of increased redox reactions. **Table 11** shows the industry average vitamin stability in pelleted or extruded feed storage over time (BASF, 2018). Note that the fat soluble vitamins (A, D, E, and K) and vitamin C (ascorbic acid) are much more susceptible to vitamin potency losses (decreased retention) over extended storage than the B vitamins. Therefore, although specific holding times for vitamin containing premixes and feeds may be effective for inactivating ASFv if it is present, it could also lead to reduced vitamin potency and nutritional value, depending on the environmental temperatures during the holding time. Selecting the vitamin product forms that are intended to improve the stability of these vitamins is an important consideration.

Table 10. Comparison of average vitamin stability (% of original potency) after pelleting at 66-70°C and 106-110°C, and extrusion at 141-145°C (adapted from BASF, 2018)

Vitamin	**Pelleting, 66-70°C**	**Pelleting, 106-110°C**	**Extrusion, 141-145°C**
Vitamin A beadlet cross-link	98	83	62
Vitamin A beadlet non-S. cong. non-XL	87	57	40
Vitamin D_3 beadlet (A/D_3) cross-link	97	89	86
Vitamin D_3 S. congealed beadlet	96	83	83
Vitamin D_3 SD	95	77	57
Vitamin D_3 drum dried	94	73	66
Vitamin E acetate, 50% silica	97	88	81
Vitamin E alcohol, natural	75	23	5
MSBC	80	44	20
MSB coated	85	60	36
MSB	70	31	7
MNB	86	62	38
MPB	82	55	30
Thiamin HCl	93	63	50
Thiamin mono	96	77	77
Riboflavin	95	78	91
Pyridoxine HCl	94	75	73
Vitamin B_{12}	99	94	86
Calcium pantothenate	95	78	75
Folic acid	95	77	64
Biotin	95	77	63
Niacin	96	80	64
Niacinamide	94	76	60
Ascorbic acid	65	25	5
Ethylcellulose coated ascorbic acid	67	30	10
Fat coated ascorbic acid	85	60	38
Ascorbyl phosphate	97	89	83
Choline chloride	99	95	94

Table 11. Industry average vitamin retention (% of original potency) in pelleted or extruded feed storage over time (adapted from BASF, 2018)

Vitamin	1 month	6 months	12 months	Average loss per month, %
Vitamin A beadlet cross-link	94	70	40	7.6
Vitamin A beadlet non-S. cong. non-XL	86	25	0	28.8
Vitamin D_3 beadlet (A/D_3) cross-link	95	80	45	6.7
Vitamin D_3 S. congealed beadlet	95	80	45	6.7
Vitamin D_3 SD	92	71	30	10.0
Vitamin D_3 drum dried	90	65	29	10.2
Vitamin E acetate, 50% silica	96	77	67	3.4
Vitamin E alcohol, natural	35	0	0	28.4
MSBC	82	30	5	22.1
MSB coated	87	50	25	11.4
MSB	60	5	0	27.7
MNB	84	45	31	9.7
MPB	76	40	24	11.7
Thiamin HCl	80	43	45	6.8
Thiamin mono	88	60	55	5.1
Riboflavin	92	54	78	2.1
Pyridoxine HCl	95	59	67	3.5
Vitamin B_{12}	92	70	67	3.5
Calcium pantothenate	97	82	81	1.8
Folic acid	92	53	58	4.6
Biotin	93	68	81	1.8
Niacin	94	79	81	1.7
Niacinamide	94	70	71	2.9
Ascorbic acid, crystalline	82	26	0	27.3
Ethylcellulose coated ascorbic acid	84	20	0	29.4
Fat coated ascorbic acid	87	35	17	14.0
Ascorbyl phosphate	95	80	62	4.1
Choline chloride	99	90	92	0.7

It is unknown if eBeam irradiation may be effective in inactivating the ASFv, as has been shown for PEDV (Trudeau et al., 2016), nor the effects, if any on vitamin stability. However, the relatively high cost and impracticality of using irradiation for potentially decontaminating premixes make this possible approach infeasible.

African Swine Fever virus is also inactivated at pH < 3.9 or > 11.5 in serum-free medium (OIE, 2009), but these extremes in pH are not found in feed ingredients or complete feeds, and additions of acids or bases would likely not only affect diet palatability, but also reduce vitamin stability. While most vitamins are stable at pH between 5.5 to 7.5, vitamin A, D_3, pantothenic acid, and folic acid are very sensitive to acidic pH, while vitamin E, K, thiamin, riboflavin, pyridoxine, and ascorbic acid are very sensitive to basic pH (BASF, 2000).

Several chemicals have been shown to be effective in inactivating ASFv. This virus is susceptible to ether and chloroform (OIE, 2009), and is inactivated by using 1% formaldehyde, 0.03% to 0.0075% sodium hypochlorite, 2% caustic soda solution, formic acid and glutaraldehyde, 1% sodium or calcium hydroxide, phenols (lysol, lysephoform, and creolin), Virkon (1:100), Lysoformin, Desoform, Octyldodeceth-20, and organic acids (Shairai et al., 2000; Gallina and Scagliarini, 2010). While these chemicals at these concentrations may be useful for cleaning and sanitizing trucks and surfaces, they cannot be used in treating contaminated feed. **Table 12** provides a list of U.S. Environmental Protection Agency registered disinfectant products for use in livestock buildings, equipment, transport vehicles, show baths and human footwear against ASFv (USDA APHIS, 2011).

Table 12. Chemical disinfectants registered by the U.S. Environmental Protection Agency for use against African Swine fever virus (adapted from Juszkiewicz et al., 2019)

EPA Registration No.	**Product Name**	**Manufacturer**	**Acive Ingredients**
11-25	Pheno-Cen Germicidal Detergent	Central Solutions, Inc.	o-phenylphenol, potassium salt p-tert-amylphenol, potassium salt potassium 2-benzyl-4-chlorophenate
211-62	Low pH Phenolic 256	Central Solutions, Inc.	o-phenylphenol, 2-benzyl-4-chlorophenol
69470-37	Clearon Bleach Tablets	Clearon Corp.	Sodium dichloro-s-triazinetrione
71654-6	Virkon S	E.I. du Pont de Nemours & Company	Sodium chloride, potassium peroxymonosulfate
71847-2	KlorKleen	Medentech Ltd.	Sodium dichloro-s-triazinetrione
71847-6	Klorsept	Medentech Ltd.	Sodium dichloro-s-triazinetrione

Unfortunately, the minimum infectious dose of ASFv is very low and has been determined to be 10^0 50% tissue culture infectious dose ($TCID_{50}$) in liquid and 10^4 ($TCID_{50}$) for a one-time exposure in feed (Niederwerder et al., 2019). These researchers also reported that the median infectious dose was $10^{1.0}$ $TCID_{50}$ in liquid and $10^{6.8}$ $TCID_{50}$ in feed, with higher doses required for infection in plant-based feed ingredients (Niederwerder et al., 2019). The ASFv is very unique (large double stranded DNA virus) in its structural, replication, and repair characteristics compared with single stranded DNA, double stranded RNA, and single stranded RNA viruses, which makes it very stable and extremely difficult to completely inactivate under practical conditions to avoid risk of infection (Declan Schroeder, personal communication). Because of these unique properties, use of published data for RNA virus inactivation to predict ASFv inactivation is not a valid approach (Declan Schroeder, personal communication).

Summary of potential risk factors for ASF virus contamination/transmission in the vitamin supply chain

1. Purchasing vitamin products from unconventional brokers and traders that do not provide necessary documentation of country of origin, quality assurance, and sanitary transport procedures.
2. Cross-contamination of vitamin premixes from imported feed ingredients (especially porcine derived) and pet foods in multi-species commercial feed mills.
3. Use of gelatin derived from pigskin when manufacturing vitamin A and D_3.
4. Use of ground corn cobs as a carrier during the choline chloride manufacturing process.

Length of time involved with chain of custody (up to 120 days) and common holding times (up to 180 days) in commercial premix facilities exceeds required holding time for 99.99% virus degradation (up to 39 days; SHIC, 2019).

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Acknowledgements

Much of the content of this manuscript is a compilation of information obtained from the major U.S. vitamin and premix manufacturers and importers obtained during the African Swine Fever-Vitamin Supply Chain Workshop conducted at the University of Minnesota on April, 29, 2019. We appreciate the many contributions of the following workshop participants:

University of Minnesota - Dr. Jerry Shurson, Dr. Pedro Urriola, Dr. Jennifer van de Ligt, Dr. Declan Schroeder, Ms. Michaela Trudeau, and Dr. Daniella Schettino

READYinc. - Ms. Polly Ligon Sullivan

Swine Health Information Center - Dr. Paul Sundberg

National Pork Board - Dr. Dave Pyburn

National Pork Producers Council - Dr. Liz Wagstrom

American Association of Swine Veterinarians - Dr. Harry Snelson

American Feed Industry Association - Ms. Leah Wilkinson

Adisseo - Mr. Phil Kemp

ADM - Ms. Camissa Hummel, Dr. Dan Jones

Cargill - Ms. Brigette Shelley

DSM - Dr. Jon Bergstrom**,** Ms. Marg Wheeler**,** Ms. Joan Ji

JNJ Oriental - Mr. Jonathan Gillaspie

Land O' Lakes/Nutra Blend - Ms. Kayla Knudsen, Dr. Aileen Joy (AJ) Mercado, Dr. Ben Warren, Mr. Gabe Adcock

VitaPlus - Mr. Al Gunderson

Additional information was obtained from published vitamin company references, peer-reviewed scientific journal publications, and personal communications. Special thanks to Dr. Jon Bergstrom (DSM), Mr. Jon Gillespie (JNJ Oriental), Mr. Phil Kemp (Adisseo), Dr. Mike Coehlo (BASF), and Ms. Brigette Shelley (Cargill) for their many valuable additional technical contributions to this report.

We also thank Dr. Jon Bergstrom (DSM), Dr. Fernando Sampedro (University of Minnesota), Dr. Paul Sundberg (Swine Health and Information Center), Dr. Jennifer van de Ligt University of Minnesota), Dr. Ben Warren (Land O' Lakes), and Ms. Brigette Shelley (Cargill) for their thoughtful comments and critical review of this manuscript.

Appendix 1. Major vitamin manufacturing companies, vitamin products, and manufacturing location.

Table A1.1. Adisseo vitamin products, trademark, and country of manufacturing

Vitamin	Trademark	Manufacturing Location
Vitamin A	Microvit® A Supra 1000	France
Vitamin AD_3	Microvit® AD_3 Supra 1000-200	France
Vitamin E	Microvit® E Promix 50	France or China
Vitamin B_7 (biotin)	Microvit® B_7 Promix Biotin 2%	France or China

Table A1.2. Adisseo vitamin products manufactured by partner suppliers, trademark, and country of manufacturing

Vitamin	Trademark	Manufacturing Location
Vitamin D_3	Microvit® D_3 Promix 500	China
Vitamin K_3	Microvit® K_3 Promix MNB 96%	China
Vitamin B_1 (thiamin)	Microvit® B_1 Promix Thiamin Mono	China
Vitamin B_2 (riboflavin)	Microvit® B_2 Supra 80	Germany
Vitamin B_3 (niacin)	Microvit® B_3 Promix Niacin	China or Switzerland
Vitamin B_3 (niacinamide)	Microvit® B_3 Prosol Niacinamide	China
Vitamin B_5 (pantothenic acid)	Microvit® B_5 Promix D-Calpan	China
Vitamin B_6 (pyridoxine)	Microvit® B_6 Promix Pyridoxine	China
Vitamin B_7 (biotin)	Microvit® B_7 Promix Biotin 10%	France
Vitamin B_7 (biotin)	Microvit® B_7 Promix Biotin 98.5%	China
Vitamin B_9 (folic acid)	Microvit® B_9 Promix Folic Acid	China
Vitamin B_9 (folic acid)	Microvit® B_9 Supra 100	China
Vitamin B_{12}	Microvit® B_{12} Promix 10000	China

Table A1.3. BASF vitamin products, trademark, and country of manufacturing

Vitamin	Trademark	Manufacturing Location
Vitamin A	Lutavit® A 500 Plus Lutavit® A 500 S NXT Lutavit® A 1000 NXT Lutavit® A palmitate Lutavit® A propionate	Germany
Vitamin AD_3	Lutavit® A/D_3 1000/200	Germany
Vitamin E	Lutavit® E 50 Lutavit® E 50 S	Germany
Vitamin B_2 (riboflavin)	Lutavit® B_2 SG80	S. Korea
Vitamin B_5 (pantothenic acid)	Lutavit® Calpan 98%	Germany
Choline chloride	Lutavit® Choline chloride	Germany

Table A1.4. DSM vitamin products, trademark, and country of manufacturing

Vitamin	Trademark	Manufacturing Location
Vitamin A	ROVIMIX® A 1000 ROVIMIX® AD_3 1000/200 ROVIMIX® A 500 WS	Sisseln, Switzerland Sisseln, Switzerland Village-Neuf, France
Vitamin D_3	ROVIMIX® D_3 500 SD ROVIMIX® D_3 500 SD ROVIMIX® HY-D 1.25% SD	Village-Neuf, France Belvidere, NJ, USA Belvidere, NJ, USA
Vitamin E	ROVIMIX® E 50% ADS ROVIMIX® E 50% ADS ROVIMIX® E 50% SD ROVIMIX® E 50% SD	Belvidere, NJ, USA Sisseln, Switzerland Village-Neuf, France Belvidere, NJ, USA
Vitamin B_1 (thiamin)	ROVIMIX® B_1	Grenzach, Germany
Vitamin B_2 (riboflavin)	ROVIMIX® B_2 80 SD	Grenzach, Germany
Vitamin B_5 (pantothenic acid)	ROVIMIX® Calpan	Daliry, Scotland
Vitamin B_6 (pyridoxine)	ROVIMIX® B_6	China
Vitamin B_7 (biotin)	ROVIMIX® Biotin ROVIMIX® Biotin ROVIMIX® Biotin HP ROVIMIX® Biotin HP	Village-Neuf, France Belvidere, NJ, USA Village-Neuf, France Belvidere, NJ, USA
Vitamin B_9 (folic acid)	ROVIMIX® Folic 80 SD ROVIMIX® Folic 80 SD	Village-Neuf, France China
Vitamin C	ROVIMIX® Stay-C® 35 ROVIMIX® Stay-C® 50 ROVIMIX® C-EC	Village-Neuf, France Village-Neuf, France Daliry, Scotland
Beta-carotene	ROVIMIX® Beta-carotene 10%	Village-Neuf, France

Table A1.5. DSM vitamin products manufactured by partner suppliers and country of manufacturing

Vitamin	Trademark	Supplier	Manufacturing Location
Vitamin B_3 (Nicotinates)	ROVIMIX® Niacin ROVIMIX® Niacinamide	Lonza Lonza	Switzerland China
Vitamin K_3	MPB	Dirox	Uruguay
	MNB	Brother Enterprises Chongqing Minfeng Dirox	China China Uruguay
	MSBC	Brother Enterprises Chongqing Minfeng Dirox	China China Uruguay
Vitamin B_{12}	Vitamin B_{12}	Sanofi-Aventis	France

Table A1.6. Company, web site, and manufacturing location (province), of vitamin products produced in China

Vitamin product	Company	Manufacturing location (province)
Vitamin A	Zhejiang Medicine Co., Ltd. http://www.china-zmc.com.cn/en/index.php?c=about&m=company	Zhejiang
	Zhejiang NHU Company, Ltd. http://www.cnhu.com/en/	Shandong and Zhejiang
	Xiamen Kingdomway Vitamin Inc. http://kdw-usa.com/	Fujian
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
Vitamin D_3	Zhejiang Medicine Co., Ltd. http://www.china-zmc.com.cn/en/index.php?c=about&m=company	Zhejiang
	Xinfa Pharmaceutical Co., Ltd. http://www.sdxinfa.cn/abouten/id/1.html	Shandong
	Zhejiang NHU Company, Ltd. http://www.cnhu.com/en/	Shandong and Zhejiang
	Xiamen Kingdomway Vitamin Inc. http://kdw-usa.com/	Fujian
	Zhejiang Garden Biochemical High-Tech Co., Ltd. http://en.hybiotech.com/index/FrontColumns_navigation01-1478744982367FirstColumnId=49.html	Zhejiang
	Taizhou Hisound Chemical Co., Ltd. http://www.hisoundpharma.com/en/us.aspx	Zhejiang
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
Vitamin AD_3	Zhejiang Medicine Co., Ltd. http://www.china-zmc.com.cn/en/index.php?c=about&m=company	Zhejiang
	Zhejiang NHU Company, Ltd. http://www.cnhu.com/en/	Shandong and Zhejiang
	Xiamen Kingdomway Vitamin Inc. http://kdw-usa.com/	Fujian
Vitamin E	Zhejiang Medicine Co., Ltd. http://www.china-zmc.com.cn/en/index.php?c=about&m=company	Zhejiang
	Zhejiang NHU Company, Ltd. http://www.cnhu.com/en/	Shandong and Zhejiang
	Nenter & Co., Inc. http://www.hxchem.net/English/companydetailnenter.html	Hubei
	Jilin Beisha Pharmaceutical Co., Ltd. http://www.jilinbeisha.com/	Jilin
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
Vitamin K_3	Brother Technology Co., Ltd. Haining Peace Chemical Co. http://www.peacechem.com/company-e/id/12.html	Zhejiang
Thiamine (B_1)	Jiangsu Brother Vitamin Co., Ltd. http://www.brother.com.cn/en/About_Subsidiary.aspx	Jiangsu
	Xinfa Pharmaceutical Co., Ltd. http://www.sdxinfa.cn/abouten/id/1.html	Shandong
	Jiangxi Tianxin Pharmaceutical Co. http://www.jxtxpharm.com/main_en.html	Shanghai
	Huazhong Pharmaceutical Co. Ltd.	Guangdong

	http://www.hpchuazhong.com/home/cn/	
Riboflavin (B_2)	Hubei Guangji Pharmaceutical Co., Ltd. http://guangjipharm.com/en/index.asp	Hubei
	Xinfa Pharmaceutical Co., Ltd. http://www.sdxinfa.cn/abouten/id/1.html	Shandong
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
	Shandong NB Technology Co., Ltd http://www.nbgroup.cn/En/	Shandong
Niacinamide (B_3)	Lonza Guangzhou Nasha, Ltd. https://www.lonza.com/custom-manufacturing/capabilities-overview/our-sites/guangzhou-nansha-china.aspx	Guangdong
	Jiangsu Brother Vitamin Co., Ltd. http://www.brother.com.cn/en/About_Company.aspx	Jiangsu
	Zhejiang Lanbo Biotechnology Co., Ltd. http://en.lanbobio.com/#	Zhejiang
	Shandong Kunda Biotechnology, Ltd. http://www.kunda-bio.com/about_e.html	Shandong
	Anhui Redpont Biotechnology Co., Ltd. http://www.china-redpont.cn/en/	Anhui
D-Calcium pantothenate (B_5)	Hangzhou Xinfu Science & Technology Co., Ltd. http://en.yifanyy.com/zhejiang_center.html	Zhejiang
	Xinfa Pharmaceutical Co., Ltd. http://www.sdxinfa.cn/abouten/id/1.html	Shandong
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
	Brother Enterprises Holding Co., Ltd. http://www.brother.com.cn/en/About_Company.aspx	Zhejiang
Pyridoxine (B_6)	Xinfa Pharmaceutical Co., Ltd. http://www.sdxinfa.cn/abouten/id/1.html	Shandong
	Jiangxi Tianxin Pharmaceutical Co. http://www.jxtxpharm.com/main_en.html	Shanghai
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
Biotin (B_7)	Fuyang Kexing Biochem Co., Ltd. http://www.kexing-biochem.com/contact_e.htm	Zhejiang
	Zhejiang NHU Company, Ltd. http://www.cnhu.com/en/	Shandong and Zhejiang
	Zhejiang Medicine Co., Ltd. http://www.china-zmc.com.cn/en/index.php?c=about&m=company	Zhejiang
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
Folic acid (B_9)	Xinfa Pharmaceutical Co., Ltd. http://www.sdxinfa.cn/abouten/id/1.html	Shandong
	Changzhou Xinhong Pharmaceutical Chemical Technology Co., Ltd. https://czxhyy88.en.ec21.com/	Jiangsu
	Nantong Changhai Food Additive Co., Ltd. http://www.niutang.com/contact/	Jiangsu
	Jiangxi Tianxin Pharmaceutical Co. http://www.jxtxpharm.com/main_en.html	Shanghai
	Jilin Beisha Pharmaceutical Co., Ltd. http://www.jilinbeisha.com/	Jilin
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
	NCPC Hebei Lexin Pharmaceutical Co. Ltd.	Hebei

Vitamin B_{12}	Xiamen Kingdomway Vitamin Inc. http://kdw-usa.com/	Fujian
	CSPC Hebei Huarong Pharmaceutical Co., Ltd. https://huarongpharma.en.ec21.com/company_info.jsp	Hebei
	Hebei Ruixin Biotechnology Co., Ltd. http://english.ruixinbiotech.com/	Hebei
	Huazhong Pharmaceutical Co. Ltd. http://www.hpchuazhong.com/home/cn/	Guangdong
Vitamin C	Shandong Tianli Pharmaceutical Co., Ltd. Vitamin Branch Company http://www.lianmengintl.com/index.php?m=about_us_factory&c=about_us_factory&a=init&id=5	Shandong
	Hebei Tianyin Biotech Co,, Ltd. http://www.hxchem.net/English/companydetailisabelzhou0106.html	Hebei
	CSPS Pharmaceutical Group., Ltd. - WeiSheng https://www.cspc.com.hk/en/global/home.php	Hebei
Choline chloride	Liaoning Biochem Co., Ltd. http://en.choline-chloride.cn/index.php	Liaoning
	Shandong NB Technology Co., Ltd http://www.nbgroup.cn/En/	Shandong
	Shandong Jujia Biotech. Co. Ltd. http://www.jujiagroup.com/en/list.php?fid=44	Shandong
	Shandong Aocter Chemical http://en.aocter.net/copyof_index.html	Shandong
	Hebei Be-Long Corporation	Hebei
Carnitine	Northeast Pharmaceutical Group Co., Ltd http://www.nepharm.com/	Shenyang

Appendix 2. Photos of vitamin manufacturing facilities in China

Source: Shandong Xinfa, No.1 Tongxing Road, Kenli, Dongying City,Shandong, China
http://www.sdxinfa.cn/abouten/id/1.html

Figure A2.1. Outdoor premises of vitamin manufacturing facility

Figure A2.2. Employee attire used to follow Good Manufacturing Practices (GMP)

Figure A2.3. Vitamins are manufactured in sanitary and well-maintained facilities

Figure A2.4. Sanitary stainless-steel vitamin product dryers

Figure A2.5. Automatic pallet packing of finished vitamin product


Figure A2.6. Secure storage of finished vitamin products in warehouse

Source: Zhejiang NHU Company Ltd, No.4 Jiangbei Road, Yulin Street, Xinchang County, Zhejiang Province http://www.cnhu.com/en/

Figure A2.7. Biosecurity using dressing rooms separated from the vitamin production facility

Figure A2.8. Sanitary and well-maintained vitamin production areas

Figure A2.9. Locked, secure, and isolated raw material tanks

Appendix 3. Flow charts of examples of various vitamin production processes

Figure A3.1. Vitamin A 650 (feed grade) production process
Source: Zhejiang Medicine Co., Ltd.

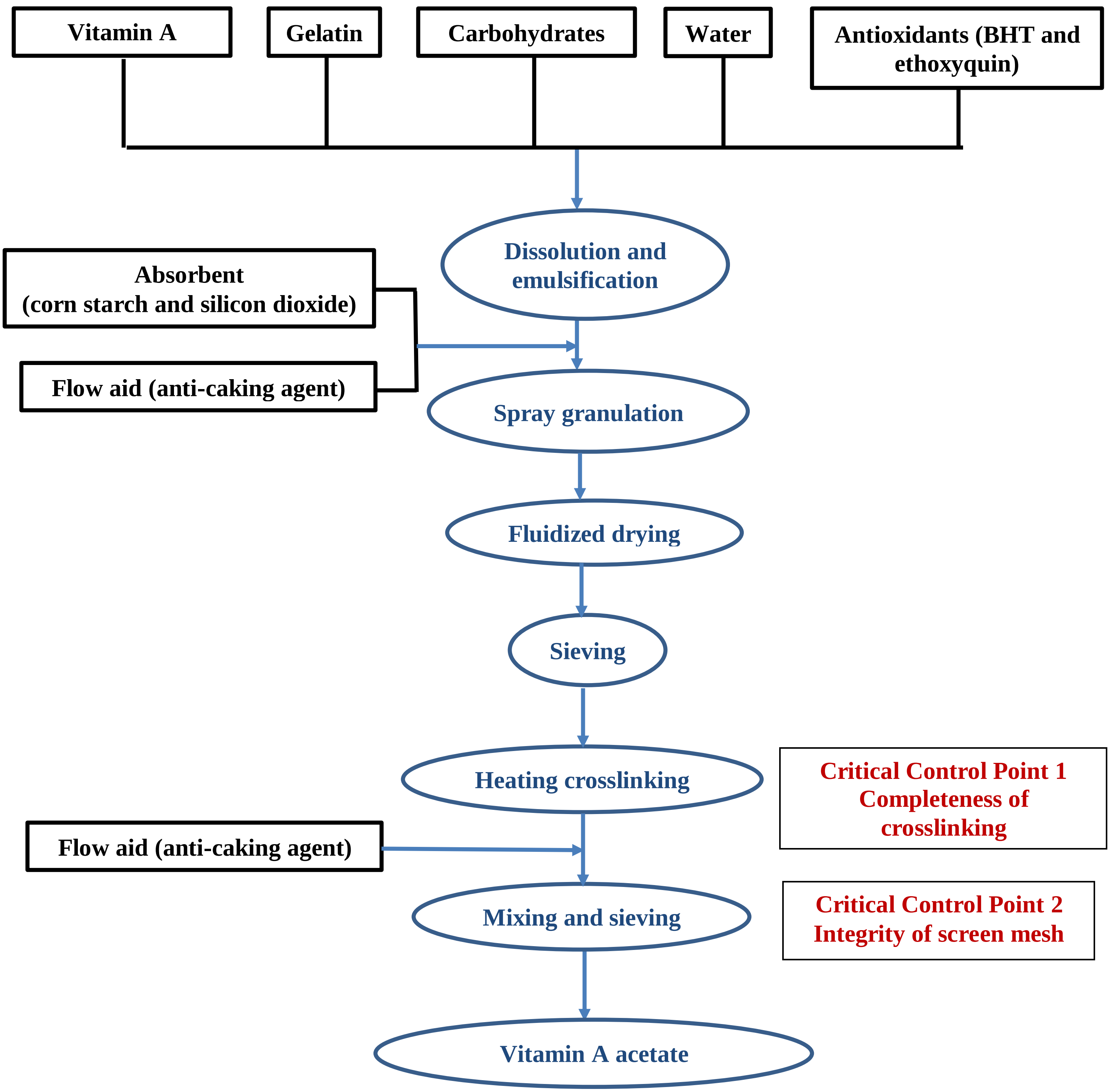

Figure A3.2. Vitamin A 1000 (feed grade) production process
Source: Zhejiang Medicine Co., Ltd.

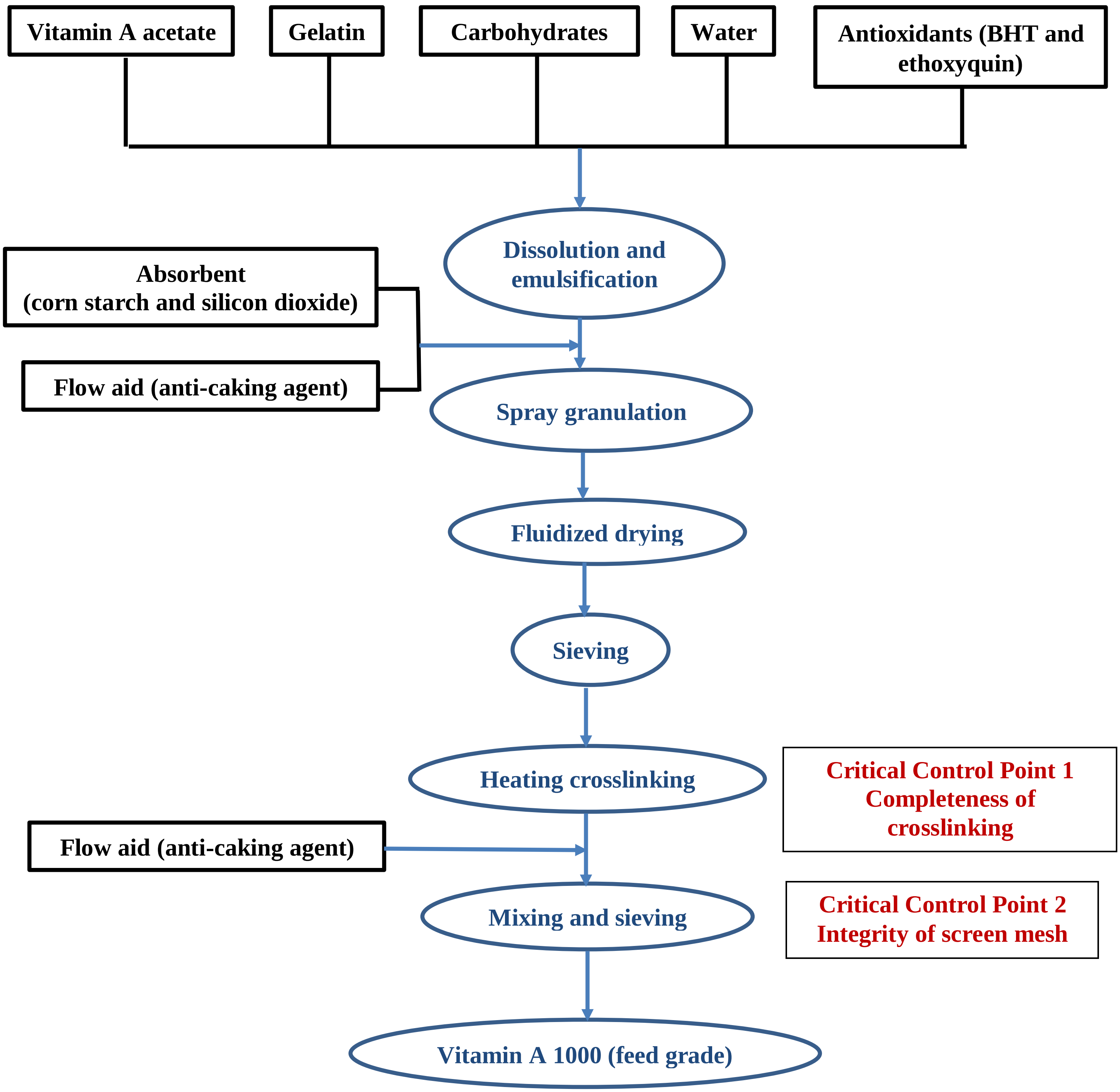

Figure A3.3. Vitamin D_3 500 (feed grade) production process
Source: Zhejiang Medicine Co., Ltd.

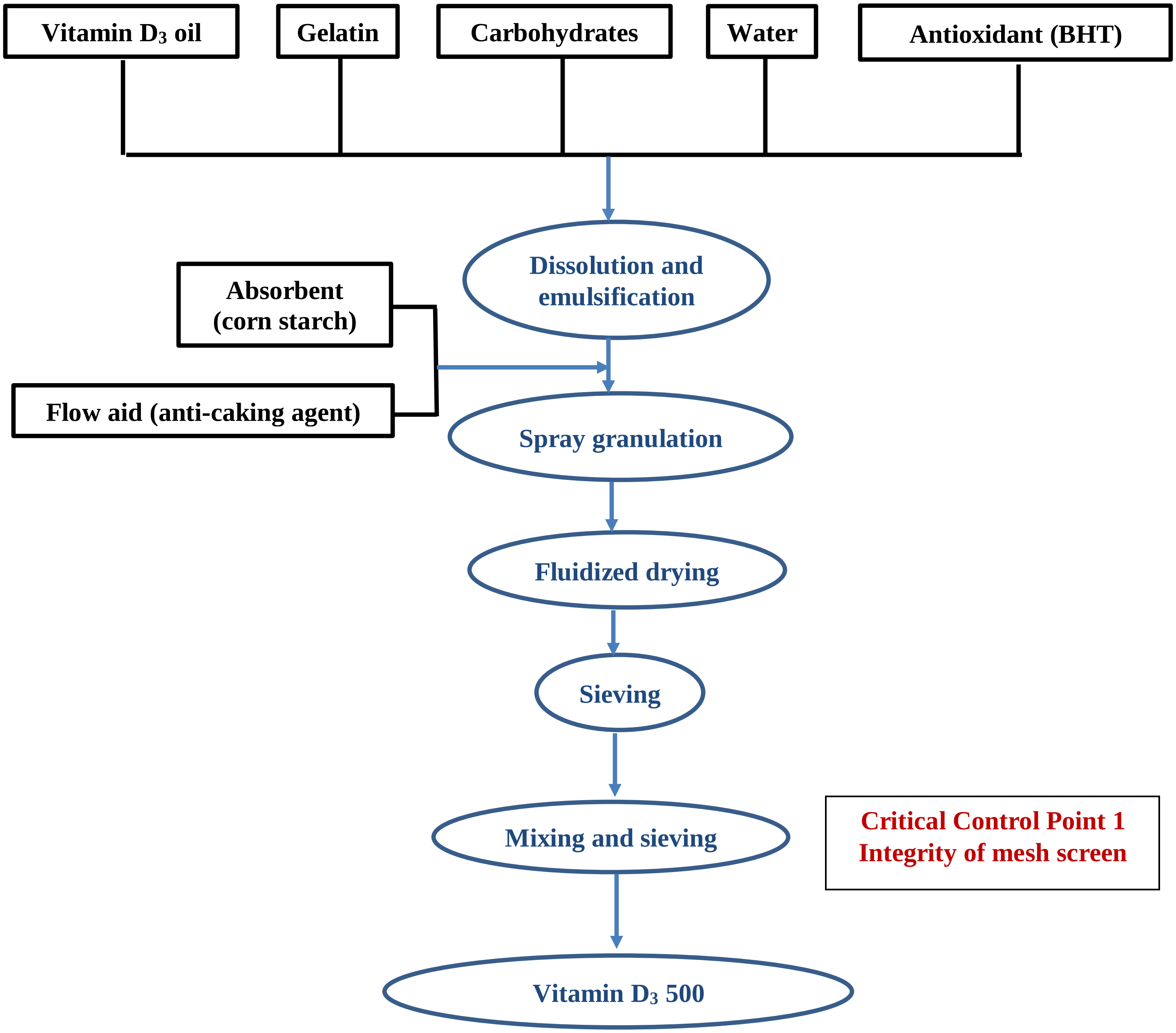

Figure A3.4. Vitamin E/all-rac-alpha-tocopheryl acetate 50% (feed grade) production process
Source: Zhejiang Medicine Co., Ltd.

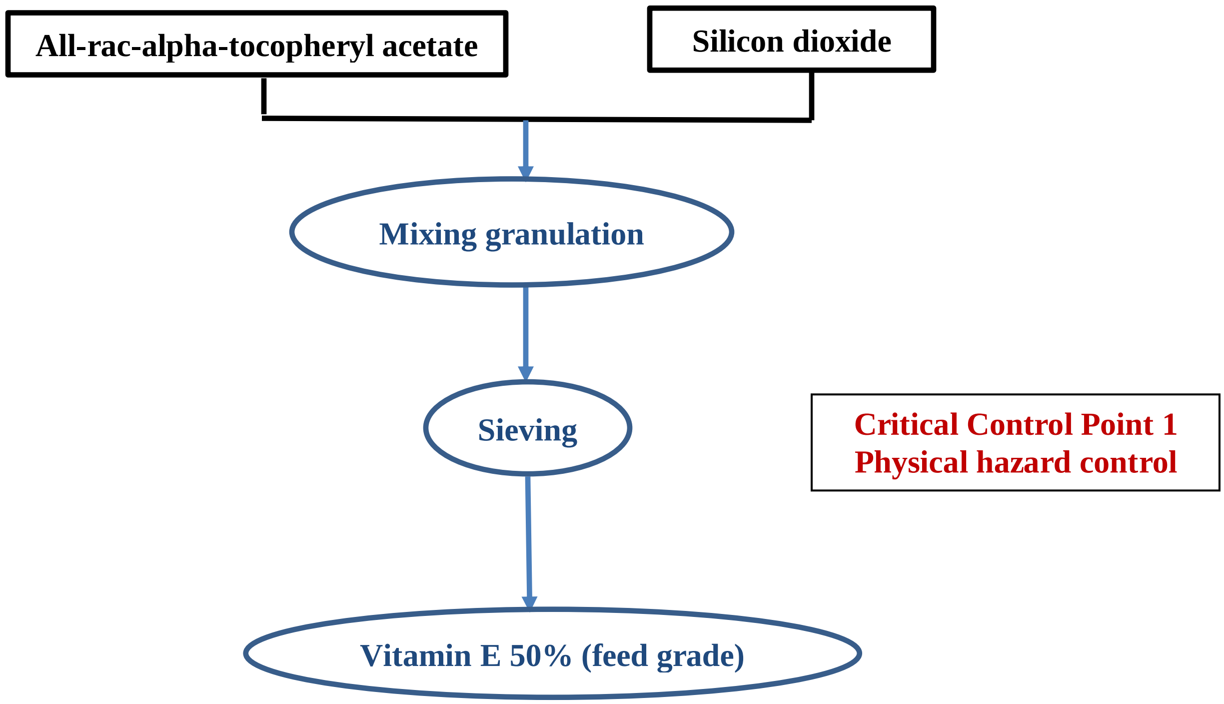

Figure A3.5. Vitamin B2 (riboflavin; 80% SD feed grade) production process
Source: Guangji Pharmaceutical (Mengzhou) Co., LTD, Mengzhou City, Henan Province, China

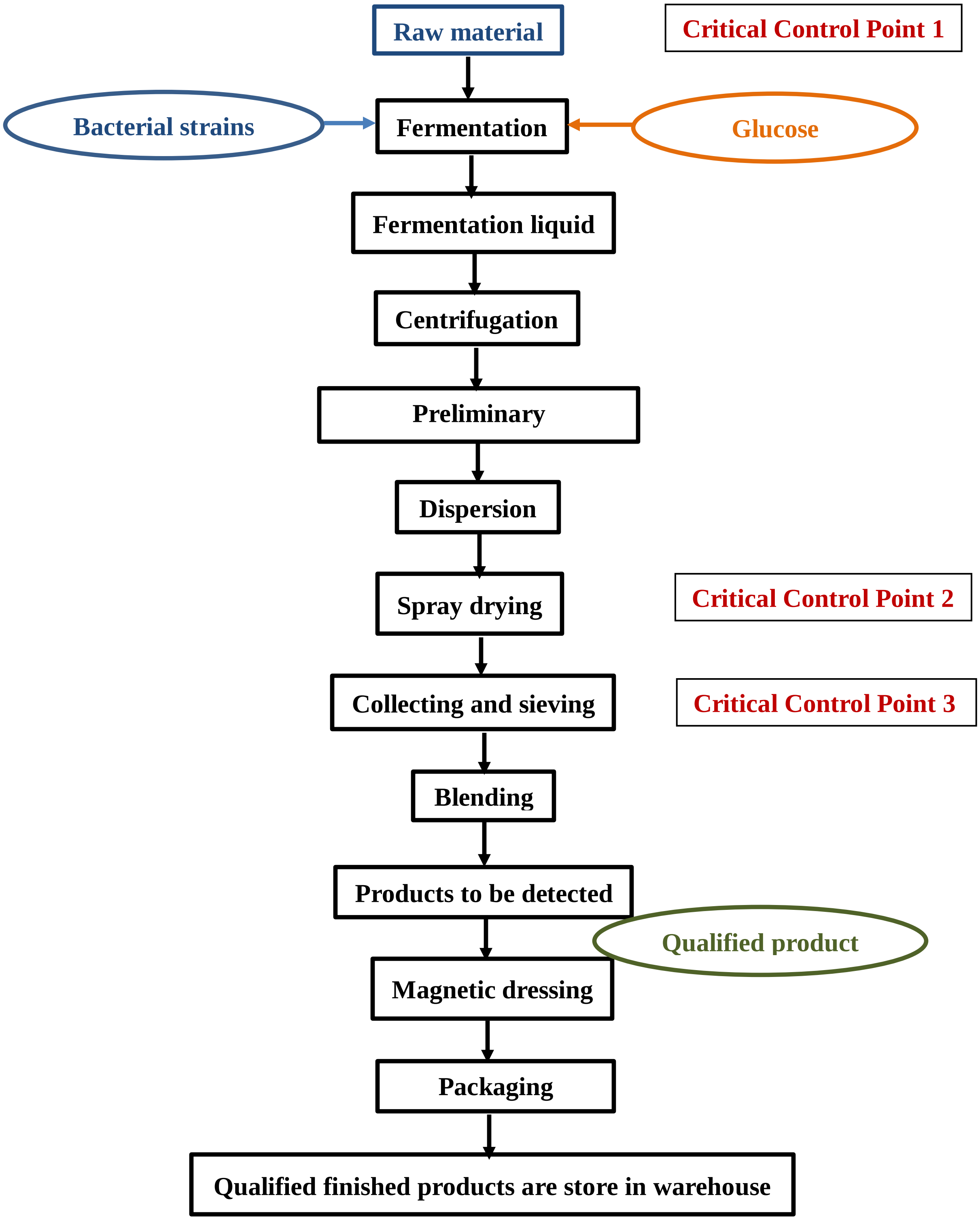

Figure A3.6. Vitamin B5 (calcium pantothenic acid) production process
Source: BASF (2018)

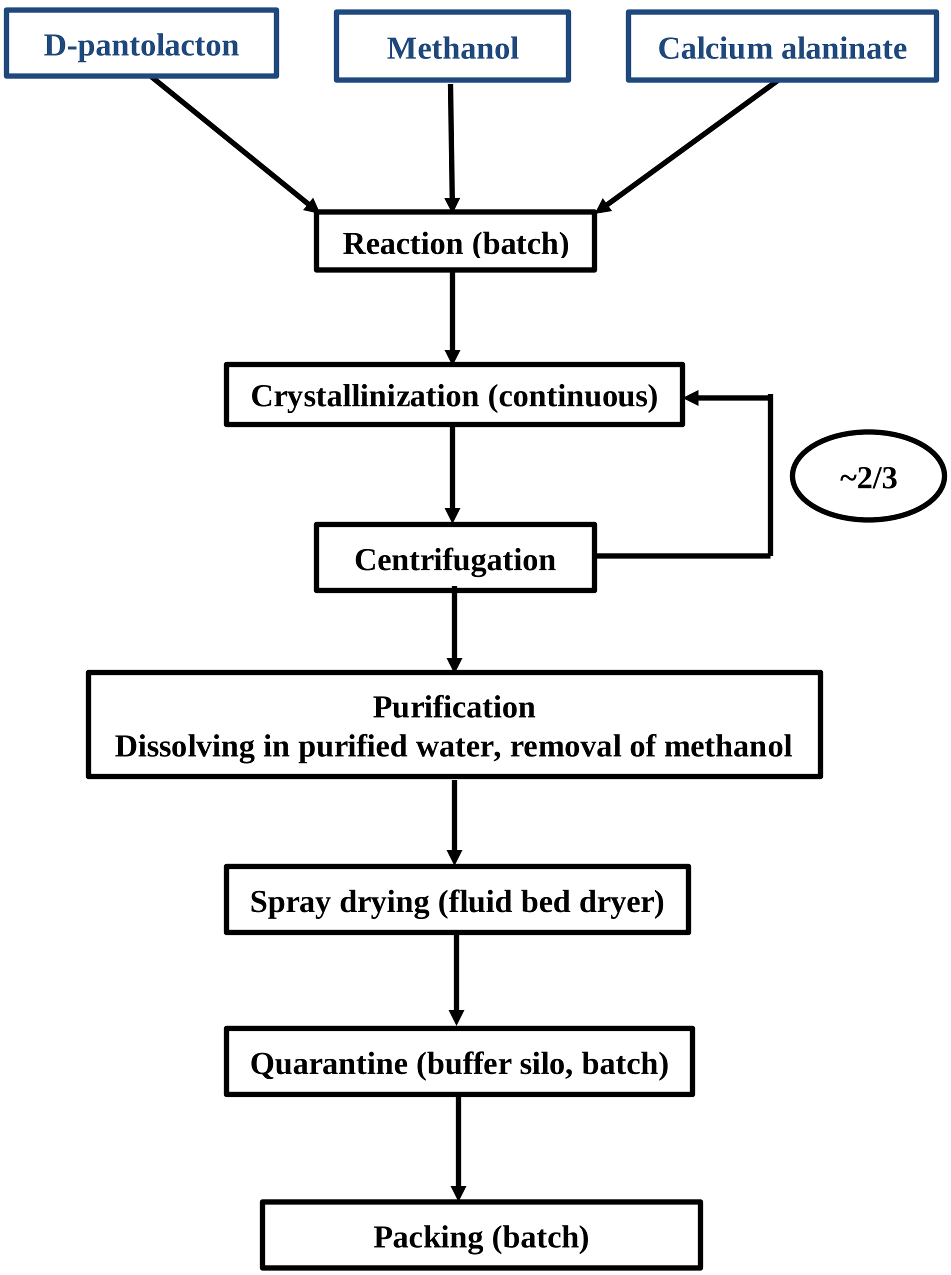

Figure A3.7. Choline chloride production process
Source: BASF (2018)

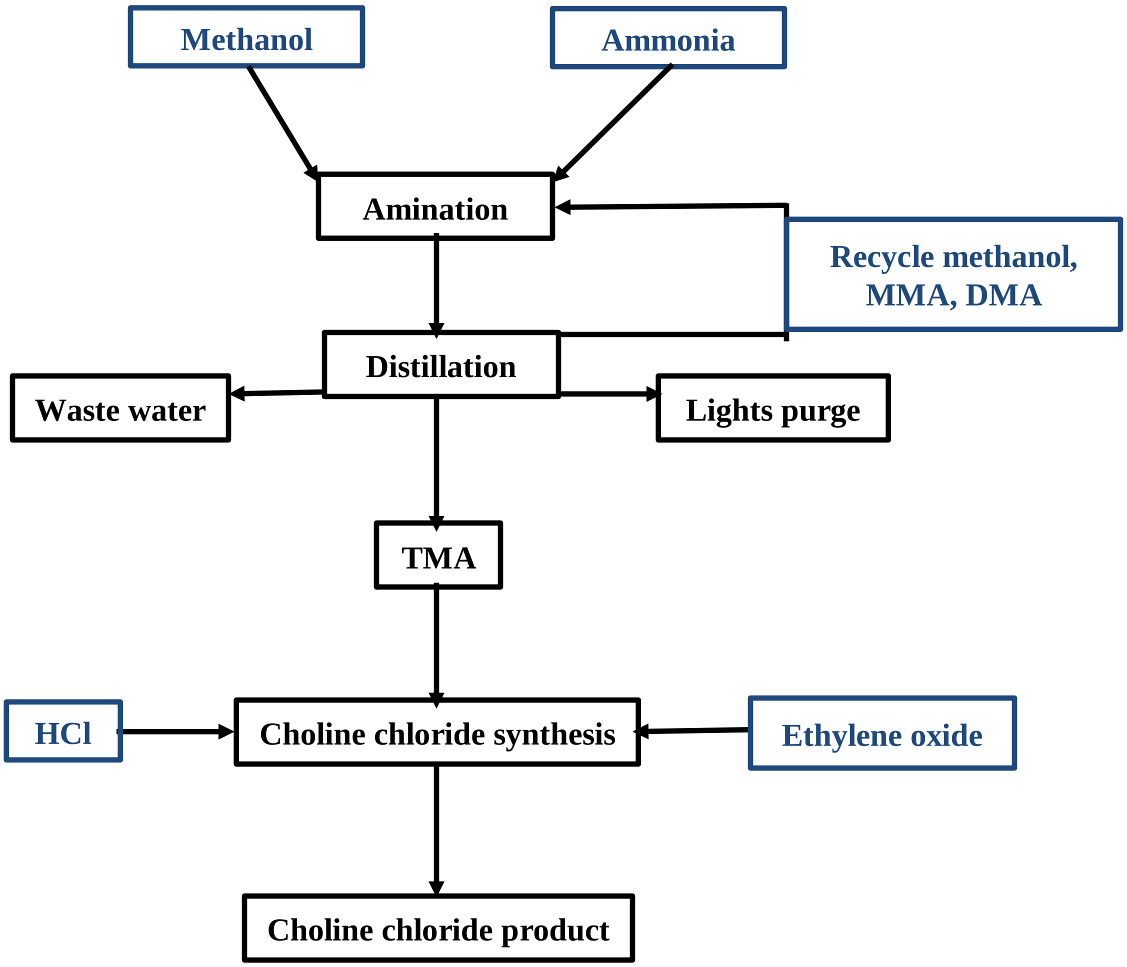

Table A3.1. Overview of key ingredients and production processes used to produce forms of vitamin K and various B vitamin products

Vitamin	Key ingredients	Process	Production stages
Vitamin K_3 (MNB)	Sodium dichromate, sulfuric acid	Synthesis	Oxidation Filtration Sulfonation Crystallization Centrifugation Washing Nicotinamide + condensation Centrifugation Drying Mixing Sieving Packing
Vitamin K_3 (MSB)	Sodium dichromate, sulfuric acid	Synthesis	Oxidation Filtration Sulfonation Crystallination Centrifugation Washing Drying Mixing with sulfuric acid Sieving Packing
Thiamine (B_1)	Thiothianmine, hydrogen peroxide	Synthesis	Cyclization Oxidation Salification Neutralization Decoloration Centrifugation Washing Drying Packing
Riboflavin (B_2)	Culture medium	Fermentation	Raw material addition Disinfection of raw material Main fermentation Centrifugation Crystallization Filtration Sieving Spray drying Blending Packing
Niacin (B_3)	3-picoline	Synthesis	Hydrolysis Filtration Neutralization Drying Milling Sieving Blending Packing
Niacinamide	3-picoline	Synthesis	Hydrolysis Filtration

			Crystallization Centrifugation Concentration Drying Sieving Packing
D-Calcium pantothenate (B_5)	Beta-alanine, methanol, calcium oxide	Synthesis	Calcification Decoloration Filtration Condensation Crystallization Centrifugation Removal of methanol Spray drying Sieving Blending Packing
Pyridoxine (B_6)	L-alanine, ethanol, oxalic acid	Synthesis	Esterification Cyclization Aromatization Hydrolysis Decoloration Crystallization Drying Milling Blending Packing
Folic acid (B_9)	NP amino benzoyl glutamic acid, 1,1,3-trichloroacetate	Synthesis	Condensation Cyclization Filtration Acid purification Alkali purification Filtration Spray drying Milling Sieving Blending Packing
Vitamin B_{12}	Culture medium	Fermentation	Raw material dumping Disinfection of raw material Main fermentation Acidification Hydrolysis Centrifugation Acidification Ion exchange Spray drying Blending Packing
Choline chloride (vegetable carrier)	Trimethylamine, hydrochloric acid	Synthesis	Neutralization Synthetic reaction Decoloration Filtration Mix with carrier Drying Sieving

			Packing
Choline chloride (silica carrier)	Trimethylamine, hydrochloric acid	Synthesis	Neutralization Synthetic reaction Decoloration Filtration Mix with carrier Packing
Choline chloride (liquid)	Trimethylamine, hydrochloric acid	Synthesis	Neutralization Synthetic reaction Decoloration Filtration Packing

Appendix 4. Examples of origin, types of carriers, and major heating processes (temperature and duration) of vitamin products manufactured by Zhejiang Medicine Co., Ltd.

Vitamin Product	**Carriers and origin**	**Heating processes (temperature and duration)**
Vitamin A 500/650/1000	Gelatin – pigskin Corn starch – corn Glucose – corn	Fluidized drying (55°C/140 minutes) Crosslinking (90-110°C/15 minutes)
Vitamin A (water dispersible) 500,000 IU/g	Arabic gum – Acacia senegal Glucose syrup – corn	Dissolving (65-85°C/> 45 minutes) Spray drying (200°C/1 minute)
Beta-carotene, 10%	Gelatin – pigskin Corn starch – corn Sugar – sugar cane	Dissolving (65-75°C/45-55 minutes) Spray drying (120-140°C/60 minutes) Fluidized drying (80°C/180 minutes)
Canthaxanthin, 10%	Gelatin – pigskin Corn starch – corn Sugar – sugar cane	Dissolving (65-75°C/45-55 minutes) Spray drying (120-140°C/60 minutes) Fluidized drying (80°C/180 minutes)
Vitamin D_3	Gelatin – pigskin Corn starch – corn Sugar – sugar cane	Emulsification (60-65°C/45 minutes) Fluidized drying (60°C/180 minutes)
Vitamin E, 50%	Silicon dioxide – quartz sand	Mixing granulation (80°C/15-20 minutes)
Vitamin E (water dispersible) 50% CWS/FG	Sodium starch octenyl succinate – corn	Dissolving (58-68°C/> 45 minutes) Spray drying (200°C/1 minute)
D-biotin, 2%	Maltodextrin – corn	Dissolving (60-65°C/40 minutes)

Appendix 5. Examples of vitamin and premix manufacturing certifications of major vitamin manufacturers

Company	Vitamin products	Certification
Adisseo	Vitamin A Vitamin AD_3 Vitamin E Biotin, 2%	FAMI-QS ISO 9001:2015, ISO 14001:2015, OHSAS 18001:2007, FSSC 22000, ISO 22000:2005, ISO 2202-1:2009 (in compliance with EU, CFIA, and U.S. FDA)
BASF	Vitamin A Vitamin AD_3 Vitamin D_3 Vitamin E B_2 (riboflavin) Calpan Choline chloride	FAMI-QS ISO 14001:2005, ISO 9001:2015/KS Q, ISO 9001:2015, ISO 50001:2011, 22000:2005
DSM	*Vitamin manufacturing* Vitamin A Vitamin E B_3 (niacinamide) B_6 (pyridoxine HCl) Folic acid MNB MSBC	FAMI-QS ISO 22000:2005 FSMA compliant (HACCP, Preventative control plan, cGMP, supply chain control, sanitary transport, and foreign supplier verification) HACCP
DSM	*Vitamin premix manufacturing*	ISO 9001:2015 FAMI-QS HACCP (in compliance with CFIA and U.S. FDA) Certified Partners in Protection security program (Canada) and Customs-Trade Partnership Against Terrorism program (U.S.)
Lonza Guangzhou Nasha, Ltd. Guangzhou, China	Niacinamide	ISO 22000:2005, ISO/TS 22002:2009, additional FSSC 22000 requirements
Xinfa Pharmaceutical Co., Ltd. Shandong, China	Vitamin D_3 beadlets D-calcium pantothenate D-panthenol B_1 thiamin HCl Folic acid B_2 (riboflavin) B_6 (pyridoxine HCl)	ISO 22000:2005, ISO/TS 22002:2009, additional FSSC 22000 requirements
Zhejiang Medicine Co., Ltd.	Vitamin A acetate acid ester Vitamin A acetate beadlets Vitamin D_3 beadlets Vitamin AD_3 beadlets Vitamin E powder D-biotin	FAMI-QS GMP+FSA HACCP

Appendix 6. Examples of vitamin manufacturers and products from China that have completed additional biosecurity audits

Company	**Products audited**
Anhui Redpont Biotechnology Co., Ltd	Nicotinamide
Brother - Haining	Vitamin K_3
Changzhou Xinhong - Jiangsu	Folic acid
CSPC HeBei Huarong Pharmaceutical Co., Ltd.	Vitamin B_{12}
CSPS Pharmaceutical Group., Ltd. - WeiSheng	Vitamin C 35%
Fuyang Kexing Biochem Co., Ltd.	Biotin
Zhejiang Garden Biochemical High-Tech Co., Ltd.	Vitamin D_3
Hubei Guangji Pharmaceutical Co., Ltd.	Vitamin B_2
Hebei Be-Long Corporation	Choline chloride
Hebei Ruixin Biotechnology Co., Ltd	Vitamin B_{12}
Hebei Tianyin Biotech Co., Ltd	Vitamin C
Taizhou Hisound Chemical Co., Ltd.	Vitamin D_3
Huazhong Pharmaceutical Co., Ltd.	Vitamins B_1 and B_6
Jiangsu Brother Vitamin Co., Ltd.	Vitamin B_1
Jiangxi Tianxin Pharmaceutical Co.	Vitamin B_1, B_6, and folic acid
Jilin Beisha Pharmaceutical Co. Ltd, - Jilin	Vitamin E and folic acid
Liaoning Biochem Co., Ltd.	Choline chloride
Nantong Changhai- Jiangsu	Folic acid
NCPC Hebei Lexin Pharmaceutical Co. Ltd	Vitamin B_{12}
Nenter & Co.,Inc	Vitamin E
Zhejiang NHU Company, Ltd.	Vitamins A, E, D_3, biotin, pigments
Shandong Aocter Chemical	Choline chloride
Shandong JuJia Biotech Co., Ltd	Choline chloride
Shandong Kunda Biotechnology Co., Ltd	Niacinamide/potassium sorbate
Shandong NB Technology Co., Ltd	Choline chloride
Shandong Tianli Pharmaceutical Co., Ltd., Vitamin Branch Company	Vitamin C
Xinfa Pharmaceutical Co., Ltd.	Folic acid, D-Calcium pantothenate, Vitamin B_1 and B_6
Hangzhou Xinfu Science & Technology Co., Ltd.	Vitamin B_5
Zhejiang Lanbo Biotechnology Co., Ltd.	Niacinamide
Zhejiang Medicine Co., Ltd.	Vitamin A, D_3, E, biotin/VE 50%, biotin