



Well-Being

Product Line Safety

Laboratoires Activa

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Introduction and Purpose

The design and manufacturing of safe and efficient dietary supplements is one of the foundations of Laboratoire ACTIVA's way of doing business on a sustainable and ethical manner globally.

The Well-Being is a full product line of 12 health condition formulated dietary supplements, based on carefully engineered blends of herbal extracts. A patented and innovative encapsulation process offers an effective gastro-protection of the active ingredients for an optimal release and absorption directly into the intestines. This controlled release mechanism allows an increased response to the active compounds, hence with a reduction in the dosage (one pill a day or infant formulations).

Well-Being products are engineered around four major concepts:

1. The sourcing of Dry Herbal Extracts among the best-in class providers globally
2. The creation of Health Condition Oriented titrated blends of the dry extracts (the Active Substance)
3. The encapsulation of the active substance around a neutral core and surrounded by a semi-permeable membrane to provide the controlled released mechanism.
4. A Hypoallergenic Capsule of marine origin (the Aquacaps^R capsule)

By presenting the processes involved in the sourcing of the raw materials and discussing the manufacturing processes involved in the manufacturing of the Well-Being products, this report addresses the potential safety concerns of the Well-Being product line.

Best in class dry herbal extracts and health condition titrated blends.

The foundation of the therapeutic effect of the Well Being resides in the engineering of health condition blends of standard dry herbal extracts. For instance, Well-Being Vitality is a blend of Ginseng, Acerola, Guarana and Pineapple dry extracts. The Well-Being Vitality's Active Substance Specification (proportion of each compound) are part of the Intellectual property of Laboratoires ACTIVA and are the foundation for the overall manufacturing and quality control process (see table 1)

SPECIFICATIONS MATIERES ACTIVES (Active Substance Specifications)					
EXTRAIT SEC	Fournisseurs	N° de lot :	Date de fab.	Titre	Spécifications
Dry extract	Provider	Batch n°	Manuf. Date	Content of matter compound	Specifications
Extrait sec de Ginseng <i>Ginseng dry extract</i>	PLANTEK	05041104	APRIL 2005	15,00%	≥ 15 % in total saponoside expressed in ginsenoside Pg1
Extrait sec d'Acerola <i>Acerola dry extract</i>	HERBS International	0011.6.11E7/117	SEPT. 2004	26,80%	≥ 25,0 % in ascorbic acid
Extrait sec de Guarana <i>Guarana seeds dry extract</i>	PREXINT	PB-00011005 GU	APRIL 2005	10,10%	≥ 10,01 % in caffeine
Extrait sec d'Ananas <i>Pineapple fruit dry extract</i>	BG PHARMA	F04113/04	MAY 2005	107 GDU	≤ 100 GDU in bromelain

Table 1: Active Substance Specification for the Well-Being Vitality product.

These raw Dry Herbal extracts are sourced from the best-in-class providers around the world. Some of Activa's providers include Plantex (France), Herbs International (USA), Prexint (USA), BG Pharma (India), and EXXENTIA (Spain). These Extracts come with their own quality control and Material Data Sheets documentations and Batch Analysis Sheets (Table 2).

About half of the Dry Herbal extracts that are used in the Well-Being product line are listed on the Botanicals FDA GRAS list, as a result of a consensus of scientific opinion¹. Many herbs are listed by the FDA because of their use in liqueurs and as components of natural flavoring prior to 1958, when the food additive regulations were written. However, alternative plants, such as flavoring water in an herbal team, are presumably also safe, and the FDA has taken no action against any product on their list.

Some additional herbs are also quoted in the FDA/NHI Drugs and Supplements fact pages².

The remaining compounds have a recognized pedigree of safety, documented by numerous clinical and toxicology studies. For instance, the safety of Curcumins has been studied and reported by the University of Lieges in 2006 and is based on Cellular death, Cellular DNA stability and Cellular Mitochondrial activity as a function of time and dose. Thanks to this In Vitro evaluation of cell viability, the study concludes that there is no Citotoxicity of the active compounds used in Well-Being Articular³.

FICHE DE DONNEES DE SECURITE
EXTRAIT SEC DE GINGEMBRE

1. IDENTIFICATION DU PRODUIT ET DE LA SOCIETE

Nom commercial : EXTRAIT SEC DE GINGEMBRE
 Nom chimique : EXTRAIT SEC DE GINGEMBRE
 Nom botanique et partie de la plante utilisée : ZINGIBER OFFICINALIS ROSCOE - rhizome
 Type de produit et utilisation : Matière première (extrait d'origine végétale) pour utilisation pharmaceutique, diététique et cosmétique.
 Identification de la société fournisseur : B.G. PHARMA (Botanical Goods Pharma)
 38 Rue St Ferdinand - 75017 Paris
 Tel: 01 53 81 9510
 Fax: 01 45 72 25 47

N° de téléphone d'appel d'urgence : 01 53 81 95 10 - B.G. PHARMA

Organisme consultatif officiel : Centre antipoisons

Extract : SAGE DRY EXTRACT 10% POLYPHENOLS Batch number : X051710-SAL
 Scientific name : Salvia officinalis L.
 Exp. date : 17/10/00
 Manufacturing Date : 11/10/02

Drug : Leaves
 Solubility : Partially soluble in hydroalcoholic solutions.
 Appearance : Olive coloured powder with non characteristic odour and taste.

ANALYSIS	SPECIFICATIONS	METHODS	RESULTS
pH	4 - 7	Co. Pharm. 02 (9 ed., 2.2.3)	4.9
Loss on drying	≤ 5.0%	Co. Pharm. 02 (9 ed., 2.2.3)	4.2%
Total ash	≤ 20%	Co. Pharm. 01 (9 ed., 2.4.2)	3.6%
Ashy matter	Min. 20%	(U.K.)	10.6% Total polyphenols
Specific weight	> 0.4 g/ml	Co. Pharm. 02 (9 ed., 2.9.10)	0.88 g/ml
Bulk density	> 0.2 g/ml	Co. Pharm. 02 (9 ed., 2.9.10)	0.410 g/ml
Particle size	> 100 microns	Co. Pharm. 02 (9 ed., 2.9.10)	1.9%
100 - 150 microns			12.0%
150 - 180 microns			84.1%
> 180 microns			
Microbiology		Co. Pharm. 02 (9 ed., 8.3)	
Total aerobic	< 10,000 /mg		Complies
Enterobacteria	< 100 /mg		Complies
Fungi and yeasts	Absence (1 g)		Complies
Staphylococcus sp.	Absence (10 g)		Complies
Streptococcus sp.	< 100 /mg		Complies
S. aureus	Absence		Complies
P. aeruginosa	Absence	Co. Pharm. 02	Complies
Residual solvents			
Heavy metals	20 ppm max.	Co. Pharm. 02 (9 ed., 2.4.8)	Complies
Lead			Complies
Asbestos			Complies
Mercury			Complies
Cadmium			Complies
Perforated	As per Pharm. 02	Co. Pharm. 02 (9 ed., 2.6.13)	Complies
Alkaloids	Absence		Complies

Storage: Store in dry place and sep away from strong light and heat

Origin : Spain

Qualification : APPROVED

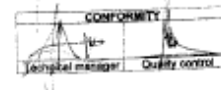


Table 2: An example of a Material Data Sheet and a Analysis Sheet for some of the Dry Extracts used by Laboratoires ACTIVA.

ACTIVA has not carried out toxicology studies for the Well Being products and relies on the fundamentals presented above to trust the safety of its product. As for any active and natural compound, rare exceptions could be observed. At this stage, not a single adverse event has been reported.

Encapsulation of the active compounds into micro-pellets or micro-granules

The encapsulation of active compounds into a semi-permeable layer and around a neutral core is a well established process in the pharmaceutical industry to better control dosage, by creating released control mechanisms for drugs to improve overall efficacy^{4, 5}.

In addition, protection of the active compounds from environmental stress such as light or moisture are benefits from such encapsulation techniques, resulting in an increase in shelf life or allowing taste masking for instance⁶.

The process used by Laboratoires ACTIVA is directly derived from pharmaceutical processes, and have been qualified for such an environment.

The quality and safety of the raw materials used for the neutral core and for the rest of the “coating” and “binding” process is proven and well documented at Laboratoires ACTIVA. Because the method of production is part of the knowledge and intellectual property attached to the Well-Being product line, little details can be shared on an open

report such as this one.

The point of this discussion is that the overall encapsulation process results in a safe and stable product that provides accurate dose control of the active compound and increased stability of the finished product, reinforcing the safety and quality of the Well-Being product line.

Aquacaps Capsule

The final encapsulation of the Well-Being micro-granules is performed with the Aquacaps® capsules designed and manufactured by ROXLOR, USA⁷. Aquacaps® are produced with fish skin gelatin raised with plants, proteins and food in conformity with the European guideline 2000/766/CE JO of 4.12.2000 relative to the food of the animals. Aquacaps® conform to the European Pharmacopoeia and possess the same machine ability, stability and dissolution as regular capsules. Aquacaps® have shown to be free of allergens and odor.

Capsules undergo a continuous series of visual inspections which are performed in accordance with AFNOR procedures. Capsule tolerances are tightly controlled to reach excellent consistency of product and subsequent performance in capsule filling machines. A Quality Insurance system has been set up to be preventive and not curative. In accordance with the article L. 5311-2 of the code of the public health, the company is submitted to the control of the agency French of Sanitary Security of the Health Products (AFSSAPS). ROXLOR works according to their manual quality, in conformity with the BPF norms (GMP) and have been certified following the ISO 9001/2000 norms. ROXOR is also FDA approved. With every delivery ROXORL provides to Laboratoires ACTIVA a bulletin of physico-chemical and bacteriological analyses in conformity with the requirements of the European Pharmacopoeia.

As a third building block of our product, the Aquacaps® capsules contribute to the safety record of the Well-Being product line.

Laboratoires ACTIVA's Quality Control overview.

Laboratoires ACTIVA's manufacturing unit in Houdan, France, have established a robust and documented manufacturing process for the Well- Being product line.

In terms of quality control, each lot of Well Being product is characterized in detail and the key quality parameters are controlled as shown on Table 2. Further storage and shipment protocol meet state of the art guidelines for dietary supplements.

FATIGUE TONUS										
GÂTULES de microgranules du mélange Fatigue Tonus <i>Pellets in capsules</i>										
NOM DU PRODUIT (PRODUCT NAME)										
MICROGRANULES	Code PF 60 6158 N° de lot : 6158 001 00									
<small>Microgranules</small>	<small>Finished Product Code</small> <small>Batch N°</small>									
Date de fabrication : 08-juil-05										
<small>Manufacturing date</small>										
SPECIFICATIONS MATIERES ACTIVES (Active Substance Specifications)										
EXTRAIT SEC	Fournisseurs N° de lot : Date de fab. Titre Spécifications									
<small>Dry extract</small>	<small>Provider</small> <small>Batch n°</small> <small>Manuf. Date</small> <small>Content of matter compound</small> <small>Specifications</small>									
Extrait sec de Ginseng	PLANTEX 05041104 AVRIL 2005 14,08% ≥ 15 % in total ginsenosides expressed in ginsenoside 101									
<small>Ginseng dry extract</small>										
Extrait sec d'Acerola	HERBS international 0011.6.11E7/117 SEPT. 2004 26,60% $\geq 25,0$ % in ascorbic acid									
<small>Acerola dry extract</small>										
Extrait sec de Guarana	PREKINT PB-00011005.GU AVRIL 2005 10,10% $\geq 10,01$ % in caffeine									
<small>Guarana seeds dry extract</small>										
Extrait sec d'Ananas	BG PHARMA F04113/04 MAY 2005 107 GDU ≤ 100 GDU in bromelain									
<small>Pineapple fruit dry extract</small>										
GELULES	Code PF R0 5158 N° de lot : 5158 001 10									
<small>Capsules</small>	<small>Finished Product Code</small> <small>Batch n°</small>									
Date de mise en gélules : 12-oct-05										
<small>Manufacturing date</small>										
Poids de remplissage en mg 375,2 mg										
<small>Filling average weight</small>										
Titre en Actifs par gélule <small>Content of Active Substance per capsule</small>										
	<small>Spécifications</small> <small>Specifications</small>									
<small>Content of Ginseng dry extract</small>	Extrait sec de Ginseng 60,0 ± 10 % 60,1 mg/caps.									
<small>Content of Acerola dry extract</small>	Extrait sec d'Acerola 15,0 ± 10 % 15,01 mg/caps.									
<small>Content of Guarana seeds dry extract</small>	Extrait sec de Guarana 15,0 ± 10 % 15,01 mg/caps.									
<small>Content of Pineapple fruit dry extract</small>	Extrait sec d'Ananas 10,0 ± 10 % 10,01 mg/caps.									
CONFORMITE AUX SPECIFICATIONS (SPECIFICATIONS COMPLIANCE)										
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">QUALITY MANAGER</td> <td style="width: 30%; text-align: center;">M. PERON</td> <td style="width: 40%;"></td> </tr> <tr> <td>DATE :</td> <td style="text-align: center;">12-10-05</td> <td style="text-align: center;">Unité de Production</td> </tr> <tr> <td>VISA :</td> <td style="text-align: center;">F. HOUDAN</td> <td style="text-align: center;">Unité de conditionnement</td> </tr> </table>		QUALITY MANAGER	M. PERON		DATE :	12-10-05	Unité de Production	VISA :	F. HOUDAN	Unité de conditionnement
QUALITY MANAGER	M. PERON									
DATE :	12-10-05	Unité de Production								
VISA :	F. HOUDAN	Unité de conditionnement								
PILULIERS	Code PF F0 5158 N° de lot : 5158 001 1_									
<small>Pillboxes</small>	<small>Code PP</small> <small>Batch n°</small>									
	Nombre de gélules par pilulier 45									
	<small>Quantity of capsules per pillbox</small>									
<small>Siège Social</small> 120, boulevard de la Colline - F-92210 Saint-Cloud Tél : 33 1 41 42 12 20 - Fax : 33 1 41 12 17 01 Siret : 401 880 273 00024	<small>Centre de Développement et Unité de Production</small> 17, rue Saint-Martin - F-92550 Boulogne Tél : 33 1 30 88 16 40 - Fax : 33 1 30 88 17 63 Siret : 401 880 273 00032	<small>Unité de conditionnement</small> 23, rue de la Frégate - F-95800 Eaubouville Tél : 33 1 39 91 31 02 - Fax : 33 1 39 91 32 10 Siret : 401 880 273 00040								
<small>SA au capital de 50 000 € - APE : 244 C - RCS : Nanterre B 401 880 273 05 b 01484</small>										

Table 3: Example of the final Quality Control and Conformity analysis sheet on a Well-Being Vitality product.

Conclusion

The design and manufacturing of safe and efficient dietary supplements is one of the foundations of Laboratoires ACTIVA's way of doing business on a sustainable and ethical manner globally.

Well Being products are engineered around four major concepts: (1) the sourcing of Dry Herbal Extracts among and best-in class providers globally, (2) the creation of Health Condition Oriented titrated blends of the dry extracts (the Active Substance) (3) the encapsulation of the active substance around a neutral core and surrounded by a semi-

permeable membrane to provide the controlled released mechanism and (4) the final “packaging” in an Hypoallergenic Capsule of marine origin (the Aquacaps® capsule) .

We have discussed the patient safety and quality control of each of these steps and established the safety profile of the Well-Being product line.

Manufacturing process and quality control analysis ensure the reproducibility and consistency of this safety profile.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

References

- ¹ Botanicals Generally Recognized As Safe : Dr James Duke taxonomic classification:
<http://www.ars-grin.gov/duke/syllabus/gras.htm>
- ² Medline all Herbs and supplements :
http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html#N
- ³ Well-Being Articular: “First Natural Anti-Inflammatory Agent Combining Strong Efficacy with Long Term Safety Data”, Laboratory ACTIVA
- ⁴ Film coated microbeads containing active compounds and method of making the same:
<http://www.patentstorm.us/patents/6432451/description.html>
- ⁵ Micro granules for pesticides and process for their manufacture:
<http://www.freepatentsonline.com/4144050.html>
- ⁶ Pharmaceutical Formulation Databases and Resources : <http://www.pformulate.com/>
- ⁷ ROXLOR LLC, USA: <http://www.roxlor.com/capsules/products.html>