Risk Management
&
Analysis Records

Sana Pharmaceutical research Co. Ltd., Steering Committee, have reviewed the different guidelines as ISO 14971:2007 and then decides to do the following as risk management for DFC cream.

Section. 1 Definitions (according to ISO 14971:2007):

Concept	Definitions
Harm	physical injury or damage to the health of people, or damage to property or the environment
Hazard	potential source of harm
Hazardous situation	circumstance in which people, property, or the environment are exposed to one or more hazard(s)
Risk	Combination of the probability of occurrence of harm and the severity of that harm.
Risk analysis	Systematic use of available information to identify hazards and to estimate risks.
Safety	Freedom from unacceptable.
Severity	Measure of the possible consequences of a hazard.

Section. 2 People that have participated in the realization of the present risk analysis:

In the realization of this analysis following people have intervened,

- Quality Manager/ Technical Manager: Samer Al-Najjar
- Quality Assurance Supervisor: Anas Awad
- Production Manager: Abdullah Al-Najjar
- Marketing Director: Nariman Saffarini

Section 3 Identification of the Qualitative and Quantitative characteristics:

User	Charge doctor, Nurse, patient
The user's formation	Patient with muscle & joint pain
Environment	Home, office, outdoors or in hospital
Special users	Children or paralyzed patient.
In contact with patient	Yes
Used material	Aqua, Honey, Olea Europeae, Fruit oil, Propylene Glycol, Arginine Hydrochloride, Ceteareth-20, Sorbitan Laurate, Cetostearyl Alcohol, Isopropyl Myristate, PEG-6 Stearate, Glycol Stearate, PEG-32 Stearate, Urea, White Petrolatum, Imidazolidinyl Urea.
Given substance and biological material tried	It doesn't proceed.

by the product	
Sterilization	It doesn't proceed. The product is non-sterile.
Susceptibility to influences of the environment	The product is given in a non-sterile state packed inside a container designed to protect the product from the environment during 3 years under the normal conditions of storage. Bad storage conditions or bad manipulation of the container may cause an injury of the product.
Fungible or essential accessories to product	It doesn't proceed. The product is supplied within a tube and neither has fungible parts no need any accessories.
Limitation in the useful life	The product is for multiple uses. Their useful life is limited at the time from its packing until its period of use with a limit of 3 years.
Slowed secondary effects associated to the lingering use	It doesn't proceed. The product is of transient use. The experience with the product has demonstrated that they don't produce long term secondary effects.
Factors that determine period of product validity	The limit of validity of the product is determined in a predominant way by the protective container. Under normal storage conditions, it is guaranteed that this container protects the product during 3 years.
A single use / re-utilizable	The product is for multiple uses.

Section 4 Identification of the possible hazards and estimate of relative risks to each hazard:

In this step we identify the possible hazards associated to the product and we evaluate and estimate the relative risk to each hazard by the means of the consideration of the probability of the hazard and the severity of the same one once happened. The hazard of a product is inherent to its technology although this risk is naturally minimized in its design and production.
The probability and the severity are coded according to the following table.

1. Classification probability hazard		
Indicator Classification	Probability	Significance
6	Frequent	Probability of big occurrence
5	Occasional	It can happen several times in the life of the system
4	Reasonably remote	It can happen at some times in the life of the system
3	Remote	Unlikely occurrence, but possible
2	Extremely remote	Occurrence probability spreading to zero
1	Physically impossible	Impossibility of the occurrence under conditions

2. Classification severity hazard		
Indicator Classification	Severity	Significance
IV 4	Catastrophic	It can cause death or lost of the product
III 3	It criticizes	It can cause severe lesion or severe injury of the product
II 2	Marginal	It can cause smaller lesions or injuries smaller than the product
I 1	Insignificant	There is neither injury to the patient nor injuries to the product

N.B for the stage of Identification of risk, they are used:

- The knowledge and the own experience
- The applicable norms

- Risk analysis checklist (according to ISO 14971:2007)

#	AP	Hazard	Prob.	Sev.	Comments
You notice: AP = applicability is in hazard, S = if, I am in hazard applicable, N = no, I am not in hazard, # = Correlative number of the hazard, Prob. = probability, Sev. = Severity					
Relative hazard to the energy					
Hazard of Biological and chemical nature					
1.	S	Biological contamination	2	II	Through the manufacturing process microbiological control is employed to maintain the microbiological specification within the limit. The product is packed in a sealed tube that prevents contamination of product through storage.
2.	S	Biological incompatibility	2	II	The used raw materials are biocompatible. They are considered remote the possibilities to cause due affections to the biocompatibility.
3.	S	Cross Infection	2	II	As device is classified as non-invasive device, It could not be a source of contamination.
4.	S	Incorrect formulation (chemical composition)	2	II	The chemical composition of the raw materials used during the manufacturing process of the device is stable, unchanged. Extensive inspections are made for the raw materials chemical composition from the stage of their incoming and into the final manufacturing stage takes place.

#	AP	Hazard	Prob.	Sev.	Comments
You notice: AP = applicability is in hazard, S = if, I am in hazard applicable, N = no, I am not in hazard, # = Correlative number of the hazard, Prob. = probability, Sev. = Severity					
5.	S	Degradation	3	III	The product is composed of: Aqua, Honey, Olea Europeae, Fruit oil, Propylene Glycol, Arginine Hydrochloride, Ceteareth-20, Sorbitan Laurate, Cetostearyl Alcohol, Isopropyl Myristate, PEG-6 Stearate, Glycol Stearate, PEG-32 Stearate, Urea, White Petrolatum, Imidazolidinyl Urea, which are not susceptible to a significant degradation during the useful life time of the product. The product is packed in a container designed to protect its content. Condition adverse storage or manipulation can cause the degradation of the container with lead to product contamination.
6.	S	Toxicity	2	II	The toxicity for components, raw materials and assembled sterilized products were conducted as a part of biocompatibility analysis.
7.	N	Pyrogenicity	-	-	The product is non-pyrogenic which was confirmed by the biocompatibility test conducted.
8.	S	Inability of maintaining the hygienic safety	2	II	The absence of appropriate conditions of hygiene when opening the product can cause the contamination of the product.
Environmental Hazard					
9.	S	Likelihood of operation outside prescribed environmental condition	2	II	The product can be used in a variety of environments including out door. No special environment is required for the use of product. To use The product in an atmosphere in the one which the conditions of cleaning and hygiene are scarce, the possibilities increase of contaminating the product during their extraction of the container before their use in the patient but it won't affect their physical properties.
10.	S	Accidental mechanical damage (injury)	3	III	The loss of mechanical integrity of the product container can causes the contamination of the product.

#	AP	Hazard	Prob.	Sev.	Comments
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11.	S	Contamination due to waste products and /or device disposal	3	III	The product form will not support spore germination or microbial growth due to their low water activity. Microbial contamination of the raw materials, ingredient water, manufacturing process, formulation, and packaging system is controlled. The testing history would include microbial monitoring during product development, scale-up, process validation, and routine testing of sufficient marketed product lots to ensure that the product has little or no potential for microbial contamination. It will not be a source of biological contamination as it will not be in contact with patient biological fluids. It doesn't need any special disposal method.
tive Hazard to operational					
12.	S	Use by unskilled/ untrained personnel	1	I	The product needs neither special skills nor training for its usage.
13.	S	Reasonably foreseeable misuse	2	I	The misuse of the device will not cause any severe injury to the patient. The instruction for use which is indicated in the label and the leaflet includes indication for all needed data to decrease the possibilities of misuse to take place.
14.	S	Incompatibility with consumable/accessories/other devices	-	-	Not applicable. The product is not dedicated to be connected with other device.
Relative Hazard to information					
15.	S	Inadequate labeling	2	II	There is adequate labeling for indications and directions , it also includes a caution not to use the product over open wounds, this will decrease the risk of the patient's infection, other cautions that is included ; for external use only, keep out of reach of children , avoid eye contact and do not use if seal or tube is injured or damaged
16.	S	Incomplete instruction for use	2	II	There is a complete information stated in the instruction for use to avoid misuse of the product. The instruction for use of the device meets the requirements of the directive 93/42/EEC and obligatory standard of the product.
17.	S	Inadequacy description of performance characteristics for the intended use	2	II	It is clearly stated to the user the intended use of the device on the label and in the instruction for use manual which supplied with the device.
18.	S	Inadequate operating instruction	2	II	The basic indications are included for correct use of the product. The cautions for correct manipulation and storage of the product.

#	AP	Hazard	Prob.	Sev.	Comments
You notice: AP = applicability is in hazard, S = if, I am in hazard applicable, N = no, I am not in hazard, # = Correlative number of the hazard, Prob. = probability, Sev. = Severity					
19.	S	Inadequate specification of pre-use checks	2	II	The integrity of the protective container and seal will be verified before opening up.
20.	S	Over complicated operating instruction	2	II	The basic indications are included in the instruction for use for correct use of the product.
21.	S	Unavailable or separated operating instruction	2	II	The basics indications are included for the correct use of the product.
22.	N	Insufficient warning of side effects	-	-	Not applicable.
23.	N	Inadequate warning of hazards likely with re-use of single use devices	-	-	The product is for multiple uses.
Hazards arising from functional failure maintenance and ageing					
24.	S	Lack of adequate determination of end device life	3	II	The inadequacy of the date of expiration could cause the use of the product while it has lost part or all of its activity.
25.	S	Loss of mechanical integrity	2	II	The loss of mechanical integrity of the product container can causes the contamination of the product.
26.	S	Inadequate packaging (contamination and/ or deterioration of the device)	2	II	A non-appropriate container may lead to the contamination of the product
27.	N	Improper re-use	-	-	The product is for multiple uses.

Section. 5 Acceptability of the Risk

Of the previous chart, we will establish a summary by means of the map of distribution of the same ones in the chart of your limit of acceptable of the risk.
The distribution of the acceptability areas and of non acceptability of the risk they have settled down with the approach that not serious acceptable all risk that could cause a serious incident in the patient y/o user. The area ALARP has settled down based on the experience.
Let us see the summary of the risks in the chart:

Probability					
	Frequent (6)				
	Occasional (5)				
	Reasonably remote (4)				
	Remote (3)		24	5, 10, 11	
	Extremely remote (2)	13	1, 2, 3, 4, 6, 8, 9, 15, 16, 17, 18, 19, 20, 21, 25, 26		
	Impossible	12			

	(1)	Insignificant (I)	Marginal (II)	Critic (III)	Catastrophic (IV)
		Severity			

Un acceptable risk	Risk "ALARP"	Acceptable Risk

Section. 6 Reduction of the risk

For the unacceptable / ALARP risk, we can control those risks by the following three ways listed (according to ISO 14971):

a) Inherent safety by design (design measure of control).
b) Protective measures in the product itself or in the manufacturing process (Protective measure of control).
c) Information for safety (Information measure of control).

#	Type of hazard	Incorrect formulation (Chemical Composition)
18	Area initial risk	ALARP Risk "As low as reasonable practiced" (P= 3; S=III)
	Ways of control	Design and protective measures.
	Methods of control	As method of design control, the manufacturing process takes place by using material of stable, unchanged chemical composition (i.e. during the manufacturing processes taking place, there is no change occur in the chemical composition of the raw material used), in which it doesn't affect the patient. As method of protective measures, extensive checks are made for the composition & concentration of raw materials used in the manufacturing process of the device from the stage of their incoming into the company, and into the final production process of packaging of the device.
	Comments	By means of the adoption of these control method / reduction of the risk, is considered that we reduce the probability of occurrence of that hazard to be physically impossible "Impossibility of the occurrence under conditions".
	Final risk	Acceptable risk P=1, S=III

#	Type of hazard	Degradation
19	Area initial risk	ALARP Risk "As low as reasonable practiced" (P=3; S=III)
	Ways of control	Protective measures.
	Methods of control	As method of protective measures, The useful life of the product comes determined by the limit of the period during which can make sure which the container of the product protects its content. We have settled down that this period is 3 years. The end of the period during which you can use the product with complete safety is indicated in the label by means of the normalized symbol and the date limit in year terms and month. The stability of the product over 3 years period has been established through accelerated stability study for 12 months at 40ºC/75 % RH.
	Comments	It is considered that when including the date of expiration of the product in the label, it reduces the probability that the product is used in the one that degradation has taken place.
	Final risk	Acceptable Risk P=1, S=III

#	Type of hazard	Toxicity
20	Area initial risk	ALARP Risk "As low as reasonable practiced" (P= 3; S=II)
	Ways of control	Protective measures
	Methods of control	As method of protective measures, Biocompatibility study takes place for all components, raw material used in the manufacturing of the device individually and assembled in the same device. The interaction of manufacturing process also controlled.
	Comments	It is considered that the adoption of these methods of control of the toxicity of the biological contamination reduces the probability of its occurrence to be physically impossible "Impossibility of the occurrence under conditions".
	Final risk	Acceptable Risk P=1, S=II

#	Type of hazard	Inability of maintaining the hygienic safety
22	Area initial risk	ALARP Risk "As low as reasonable practiced" (P=3; S=III)
	Ways of control	Design, protective measures and information.
	Methods of control	As design measure, The product is designed to be oily gel with low water activity. Presentation and keeping the device protective from the air, tissues and environment exposure.. As information measure, we incorporated to the container the normalized symbols that they indicate the storage conditions and warning are indicated of not using the product if the container has been injured or damaged. The instructions for use which supplied with each device have an indication for its optimal usage and a warning of not applying the product over open wounds and/or non intact skin.
	Comments	It is considered that when adopting these controls methods, we decrease the probability of occurrence of this hazard.
	Final risk	Acceptable Risk P=2, S=III

#	Type of hazard	Accidental mechanical damage (injury)
27	Area initial risk	ALARP Risk "As low as reasonable practiced" (P= 3; S=III)
	Ways of control	Protective measures and information.
	Methods of control	As method of protective measures, it is packed in a container that protects the content from environment and it can withstand normal condition of storage, shipping and handling while keeping its mechanical integrity. Also, as information method of control, it is included in the one labeled of the product a warning so that the user doesn't use the product if the container has been injured or damaged.
	Comments	The adoption of these control methods allows reducing the probability of occurrence of this risk.
	Final risk	Acceptable Risk P=2, S=III

#	Type of hazard	Inadequate operating instruction
39	Area initial risk	ALARP Risk "As low as reasonable practiced" (P=3; S=III)
	Ways of control	Design and protective measures.

	Methods of control	As way of design control, the instruction for use provided in the label and in the leaflet together with the warning present in simplified way the user with the proper method of product use. As way of protective measures of control, we carried out a routine confirmation of the instruction for use to meet the requirement of the recent international standards.
	Comments	It is considered that the incorporation of these measures still reduces the probability of occurrence of this risk in the absence or in the event of inadequacy of the instruction that accompany to the product.
	Final risk	Acceptable Risk P=2, S=III

#	Type of hazard	Lack of adequate determination of end device life
48	Area initial risk	ALARP Risk "As low as reasonably practiced" (P=3; S=II)
	Ways of control	Design and protective measures
	Methods of control	As design method, In the design of the product, it is determine that the useful life of the product comes limited by the useful life of the protective container. The characteristics of the materials of the container allow assigning a useful life of these of 3 years under normal condition of storage. As protective measures of control, for the control of the adaptation of the assigned expiration, accelerated stability test of the product has been conducted for 1 year at 40ºC/75 % RH. Furthermore retained samples of every batch are retested for its stability once a year and until the expiry date of the product.
	Comments	The adoption of these control methods allows reducing the probability of occurrence of this risk.
	Final risk	Acceptable Risk P=2, S=III

#	Type of hazard	Loss of mechanical integrity
49	Area initial risk	ALARP Risk "As low as reasonable practiced" (P= 3; S=II)
	Ways of control	Protective measures and information
	Methods of control	As protective measures of control, they are carried out an extensive check for the effectiveness of the protective containers which protect the content of the product. Also, as information method, it is included in the one labeled of the product a warning so that the user doesn't use the product if the container has been injured or damaged; also it is indicated in the leaflet.
	Comments	The adoption of these control methods allows reducing the probability of occurrence of this risk.
	Final risk	Acceptable Risk P=2, S=II

#	Type of hazard	Inadequate packaging (contamination and / or deterioration of the device)
50	Area initial risk	ALARP Risk "As low as reasonably practiced" (P=3; S=II)
	Ways of control	Design, protective measures and information

	Methods of control	As design control, In the design of the product we settles down that the materials of having packed will have the appropriate characteristics to protect their contents (content specification) state during storage and transport of the product throughout the product life as indicated by the manufacture and expiry date (3 years). The specification of the materials of the individual container and those of the other packaging materials (i.e. secondary packaging and transport packaging) are all documented and they are conserved in the technical file of the product. As protective measures, we carried out controls for the effectiveness of the individual container and samples of each lot of manufactured product. As information measures, The product label indicates a warning that the user doesn't use the product if the individual container has been injured or damaged; also it is included in the leaflet.
	Comments	The adoption of these control methods allows reducing the probability of occurrence of this risk.
	Final risk	Acceptable Risk P=2, S=II

Section. 7 Generation of other hazards

The methods of reduction of the established risks have been revised to determine that new risks have not been generation. The analysis of the non-conformities and incidence that you/ they can appear in the intensive operation of the team for our clients will give us in their case rules to verify that this analysis is correct.

Section. 8 Evaluation of all the identified hazards

We have carried out an exhaustive revision of the hazards that you/ they can associate to the product and therefore they are considered evaluated all the risks of the product according to the summery of the following table.

#	Hazard	Risk initial	Way control	Final risk	Other risks have been generated	Final evaluation
1	Biological contamination	acceptable		acceptable	No	ok
2	Biological Incompatibility	acceptable		acceptable	No	ok
3	Cross Infection	acceptable		acceptable	No	ok
4	Incorrect formulation (Chemical Composition)	acceptable		acceptable	No	ok
5	Degradation	ALARP	Protective measures	Acceptable Risk P=3, S=III	No	ok
6	Toxicity	acceptable		acceptable	No	ok
8	Inability of maintaining	acceptable		Acceptable	No	ok

#	Hazard	Risk initial	Way control	Final risk	Other risks have been generated	Final evaluation
	the hygienic safety					
9	Likelihood of operation outside prescribed environmental condition	acceptable		acceptable	No	ok
10	Accidental mechanical damage (injury)	ALARP	Protective measures, information	Acceptable Risk P=3, S=III	No	ok
11	Contamination due to waste products and /or device disposal	ALARP	Protective measures, information	Acceptable Risk P=3, S=III	No	ok
12	Use by unskilled/ untrained personnel	acceptable		acceptable	No	ok
13	Reasonably foreseeable misuse	acceptable		acceptable	No	ok
15	Inadequate labeling	acceptable		acceptable	No	ok
16	Incomplete instruction for use.	acceptable		acceptable	No	ok
17	Inadequacy of performance characteristics for the intended use	acceptable		acceptable	No	ok
18	Inadequate operating instruction	acceptable		acceptable	No	ok
19	Inadequate specification of pre-use checks	acceptable		acceptable	No	ok
20	Over complicated operating instruction	acceptable		acceptable	No	ok
21	Unavailable or separated operating instruction	acceptable		acceptable	No	ok
24	Lack of adequate determine of end device life	ALARP	Design , Protective measures	Acceptable Risk P=3, S=II	No	ok
25	Loss of mechanical integrity	acceptable		acceptable	No	ok
26	Inadequate packaging (contamination and/ or deterioration of the device)	acceptable		acceptable	No	ok

Section. 9 Adaptation of the safety of the product

When carrying out a revision of the previous table it is considered that the identified and the associate risks have decreased at reasonable and acceptable levels. It is considered then verified the safety of the product “Stopain plus”.

Section. 10 Conclusions:

Starting from the result of the pervious table we can conclude because that the product is safe as much for its design as for its production and it is then capable for its setting in the market.

Results of the analysis	√ Capable
	□ Not Capable

Section. 11 Changes and Revision:

When having any modification in the design of the product, when being published new applicable harmonized norms to the same one or the technologies used for their production or before the appearance of new data that you/ they can affect the evaluation of the risks, we will be carried out a revision of the present analysis to determine if they are had increasing or diminished the risks or if can be identified according to the procedure of control of changes.