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Short communication

Validation of baby cream production process

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Introduction

GMP validation is an element of quality assurance program for a pharmaceutical/biotech products or processes. To ensure that the products absolutely fit to the intended use, the company has to demonstrate in a documented form that the processes, methods, tests, activities and equipment's they deploy are capable of repeatedly producing the desired product. Therefore, each critical step in the manufacturing process must be verified to perform as intended under defined conditions (https://www.gmp7.com/blog/gmp-validation/).

After acquiring and installation of the new production equipment, scale-up of the batch size is required and a validation study should be performed for the manufacturing process (FDA, 2011).

The data acknowledged during process of production of baby cream was used during the validation of the process. The equipment used for manufacturing is of the similar design and principle of work as the previously used production machines for production of this product. The impact of the scale-up and change in the equipment was expected to be minimal on the attributes of the finished product. Previous knowledge, long-time experience and equipment manufacturer recommendations were considered to be sufficient for establishing optimal set of parameters for production. The assurance that appropriate reproducibility will be achieved will be obtained by process controls and control tests during all phases using control schedule established during the manufacturing process. The validation process included production of three batches of baby cream that were manufactured under the same conditions. The changes were documented and new version of manufacturing process was issued considering validation results and defined process parameters.

Materials and methods

All the materials used for the production of the three validation series were of same qualitative and quantitative composition as in the production of the existing equipment. The process includes aqueous phase (containing Magnesium sulfate x $7H_2O$ and Glycerin) and oil phase (containing Petrolatum and Paraffinum liquidum), waxy W/O emulsifier 1: mix of Sorbitan oleate, Hydrogenated Castor oil, Cera alba and Stearic acid with HLB value 4.5, emulsifier 2: W/O emulsifier (bland of Petrolatum, Ozokerite, Hydrogenated Castor oil, Glyceryl isostearate and Polyglyceryl-3 oleate with HLB value approx.3) additives (Phenoxyethanol, Ethylhexylglycerin) and parfum, all in prescribed quantities (Regulation (EC) No 1223, 2009).

The manufacturing process of baby cream was hot homogenization. The processing steps required for the manufacture of baby cream were defined: dissolving and mixing of the aqueous phase with excipients, melting of the oil base with excipients, loading of the oil base, merging of the two phases, mixing and cooling the homogenous mass, dispersion of the additives and homogenizations, mixing and cooling. Selected processing equipment included: double jacket mixing vessels (Olsamix150 and Melter100, OLSA S.P.A. Milan, Italy), traced hose. Process parameters (PP), set limits for every PP and acceptance criteria were also defined. PP (temperature, homogenizer speed, vacuum, mixing time, mixing speed of peripheral and central impeller) were considered as critical process parameter (CPP) in certain production phases.

Critical process parameter (CPP) in certain phases of production. Temperature was CPP for dissolving and mixing of the water phase with excipients and melting of

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the oil base with excipients. Temperature, mixing time, mixing speed of peripheral and central impeller, homogenizer speed and vacuum were CPP during the merging of the two phases and in the phase of dispersion of the additives and homogenizations.

Temperature, mixing speed of peripheral and central impeller and vacuum were CPP during final mixing and cooling.

For every phase of production, control parameters were defined. During the entire production process, visual control of the process and the mass produced is carried out.

Acceptance criteria. Each batch must meet the predetermined acceptance criteria for every phase of production. After homogenization by mixing and cooling, the product must satisfy the requirements for: appearance and color (white homogenous mass, to match an approved sample), Centrifuge Phase Separation Test (no separation should be observed), Temperature Phase Separation Test (no separation should be observed), pH value (4-7), viscosity, relative density (for information and comparison only) and microbiological quality (Total aerobic microbial count (≤ 1 × 100 CFU per 1g) absence of patogenes *Pseudomonas aeruginosa*/0.1g, *Staphylococcus aureus*/0.1g, *Candida albicans*/0.1g, Escherichia coli/0.1g) (ISO 17516, 2014).

Results and discussion

The certificates of analysis for each raw material used for manufacture of the validation batches were checked and fulfill the quality requirements.

The results of visual control indicate that clear solution was obtained for all 3 batches after dissolving and mixing of the water phase with excipients with the proposed process parameters. Thus, the proposed process parameters can be considered satisfactory for the dissolving and mixing of water phase.

The results of visual control indicate that clear solution was obtained for all 3 batches after melting of the oil phase with the proposed process parameters. Thus, the proposed process parameters can be considered satisfactory for the dissolving and mixing of oil phase.

Also, after the merging of two phases, the results of visual control indicate that homogenous mixture was obtained for all 3 batches after merging of the two phases with the achieved process parameters. Thus, the achieved process parameters can be considered satisfactory for the step merging of the two phases.

The results of visual control indicate that homogenous mixture was obtained for all 3 batches after mixing and cooling with the achieved process parameters. Thus, the achieved process parameters can be considered satisfactory for the step mixing and cooling.

The results of visual control indicate that homogenous mixture was obtained for all 3 batches after dispersion of the additives and homogenization, mixing and cooling with the achieved process parameters. Thus, the achieved process parameters can be considered satisfactory for the steps dispersion of the additives and homogenization, mixing and cooling.

Each batch met the predetermined acceptance criteria: appearance and color (white homogenous mass, matches an approved sample), Centrifuge Phase Separation Test (no separation was observed), Temperature Phase Separation Test (no separation was observed), pH value (5,60; 5,63 and 5,30 respectively for each of the three batches), viscosity (500 000 – 520 000 cp for each of the three batches), relative density (0.9542 - 0.9588 for each of the three batches), microbiological quality (TAMC 0 cfu/g for all three batches and absence of patogenes *Pseudomonas aeruginosa*/0.1g, *Staphylococcus aureus*/0.1g, *Candida albicans*/0.1g, Escherichia coli/0.1g).

Conclusion

Based on the results of three validation batches, the proposed manufacturing process for baby cream under the specified parameters is reproducible and can consistently manufacture the cream of 150.0 kg batch size with desirable quality, which meets its predetermined specifications. The impact of the scale-up and change in the equipment is considered minimal on final product quality attributes.

A new version of master production protocol has been issued with new re-established process parameters: mixing speed of peripheral impeller, homogenisation speed and vessel pressure (vacuum) in certain phases of production (ISO 22716:2007).

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