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EXAMPLE OF APPLICATION OF THE QUALITY BY DESIGN APPROACH TO THE PHARMACEUTICAL DEVELOPMENT OF A GENERIC TOPICAL GEL

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Introduction

The following work illustrates an example of application of the Quality by Design (QbD) approach to the pharmaceutical development of a generic adapalene topical gel that is therapeutically equivalent to the Reference Listed Drug (RLD).

The gel contains the active ingredient adapalene in the concentration of 0.1% w/w.
Adapalene is a retinoid indicated for the skin treatment of acne vulgaris on the face, chest, and back, where comedones, papules, and pustules predominate. Mechanistically, adapalene binds, like tretinoin, to specific nuclear retinoic acid receptors, but unlike tretinoin, not to cytosolic receptor binding proteins. Studies in human patients provided clinical evidence that cutaneous adapalene is effective in reducing the inflammatory components of acne. [1]

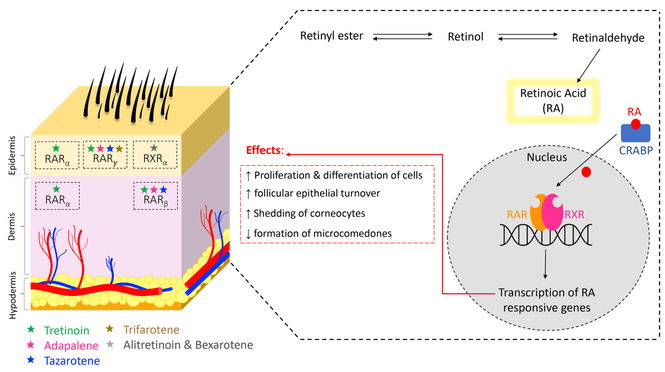

Figure 1: Biological pathway of natural retinoids and target sites of synthetic retinoids. [1]

Quality Target Product Profile (QTPP)

QTPP is described by ICH Q8 as "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product". [2]
Therefore, as first step, the Quality Target Product Profile for the generic gel was defined based on the properties of the drug substance, the characterization of the RLD product, and the consideration of the RLD label. To do so, the RLD was characterized to define the following specifications: visual appearance and texture, pH, density, relative viscosity, rheological properties such as elastic modulus G', viscous modulus G'', phase angle δ, viscosity η, yield stress, thixotropy (Reometer Haake Mars 40, Thermo scientific), PSD of the dispersed API (Mastersizer 3000, Malvern, with Hydro Mv dispersion unit), microstructure (Optical microscope Leica dm 4000). Moreover, AD assay, impurities, preservatives and EDTA (HPLC-DAD Agilent 1260) and *in-vitro* release rate (Vertical Cell Diffusion Test System HDT 1000, Copley) were determined.
For what concerned the formulation development, the quali-quantitative formulation was detailed on the basis of RLD labeling, patent literature, reverse engineering, and official foreign Ministries of Health documents.

Table 1: Quality Target Product Profile (QTPP) for generic Adapalene 0.1% gel.

QTPP Elements	Target	Justification
Dosage form	Gel	Pharmaceutical equivalence requirement: same dosage form
Route of administration	Topical	Pharmaceutical equivalence requirement: same route of administration
Dosage	0.1% w/w	Pharmaceutical equivalence requirement: same dosage
Drug product quality attributes	Physical attributes	Pharmaceutical equivalence requirement: must meet the same monographies and quality tests
	Identification	
	Assay	
	Content uniformity	
	in-vitro release rate	
	Impurities and degradation products	
	Chelating agent and preservatives assay	
	Microbial limits	
	Particle Size Distribution (PSD)	
Stability	At least 24 months	Equivalent to the stability of RLD
Container closure system	Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure product integrity.

Critical Quality Attributes (CQAs)

Afterwards, Critical Quality Attributes (CQAs) were identified based on the physicochemical properties of the RLD product.
A CQA is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality". [3]
Potential CQAs of the drug product were identified so that those product characteristics having an impact on product quality could be studied and controlled. In particular, the subset of CQAs that had the potential to be impacted by the process variables (e.g. rheological properties) were in-depth investigated during process development using tools such as the Design of Experiments. On the other hand, CQAs which were unlikely to be impacted by process variables were not analyzed in detail, but still were QTPP target elements (e.g. microbial limits), ensured through a good pharmaceutical quality system and the control strategy.

Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and their link to CQAs

Risk assessment was used throughout development to identify Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and their link to CQAs. This step was fundamental to determine which studies were necessary to achieve product and process understanding and therefore to ensure product quality.
The CMAs of the drug substance and excipients were determined through a risk assessment analysis and excipients compatibility studies.
For the CPPs, the identification started with the analysis of the manufacturing process steps in order to identify the potential variables which could have an impact on the desired quality attributes, through an Ishikawa (fishbone) diagram.

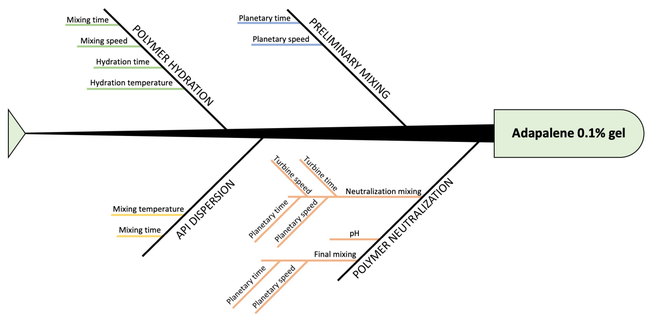

Figure 2: Ishikawa diagram of the manufacturing process of Adapalene 0.1% gel.

Then, using failure mode effects analysis (FMEA), the variables were ranked based on probability, severity, and detectability and a level of risk from low (green) to medium (yellow) to high (red) was assigned.

Table 2: Initial risk assessment of the manufacturing process for generic Adapalene 0.1% gel.

Drug Product CQAs	Process steps				
	Polymer hydration	API dispersion	Preliminary Mixing	Polymer neutralization	
				pH adjustment	Final Mixing
Particle size distribution	Medium	Medium	Low	Low	Low
Rheological properties	Medium	Low	Medium	High	High
API Assay	Low	Medium	Low	Medium	Low
pH	Low	Low	Low	Medium	Low
Content Uniformity	Medium	Medium	Medium	Low	Medium

Manufacturing process development: Design of Experiment (DoE)

The preparation of Adapalene 0.1% gel was performed in a turbo-emulsifier with a 10 kg batch size and is divided into four phases: polymer hydration, API dispersion, preliminary mixing, polymer neutralization (divided into pH adjustment and final mixing). After the risk assessment, the impact of the higher ranked variables was evaluate through Design of Experiments (DoE), to gain a greater understanding of the manufacturing process and to reduce the risk associated to those variables.
Three factors were identified as worthy to be studied through the DoE: the turbo-emulsifier's turbine speed during pH adjustment, the turbo-emulsifier's turbine time during pH adjustment, and the turbo-emulsifier's planetary time during final mixing. The probable affected CQAs were selected as DoE responses and were: the elastic modulus G', the viscous modulus G'', the phase angle δ, and the viscosity η. To analyze the effect of the independent variables and their interactions, while estimating a probable curvature of the resulting mathematical model, an RSM spherical CDD design was set up, with 6 central points, 8 factorial points, and 6 axial points.

Table 3: DoE studied parameters and their levels for generic Adapalene 0.1% gel.

Independent variable	Axial minimum level (-α)	Fractional minimum level (-1)	Central point (0)	Fractional maximum level (+1)	Axial maximum level (+α)
Turbine speed (rpm) during the pH adjustment	500	1150	2000	2850	3500
Turbine time (min) during the pH adjustment	4	9	17	25	30
Planetary time (min) during final mixing	30	55	90	125	150

From the data obtained, an optimization phase occurred. Entering the RLD characterization values as target, the DoE software (Stat-Ease Design Expert 13) can calculate the process parameters settings that give the desired product. This closeness to the optimal result is expressed with a desirability function, where a value of 1 is attributed to the target. From the solutions proposed by the software, the one with greater desirability value was chosen, corresponding to a turbine speed of 2850 rpm, a turbine time of 25 min, and a planetary time of 90 min. With these settings, three confirmation batches were produced and characterized. Their rheological values fell within the 95% prediction interval, demonstrating the predictability of the mathematical model.

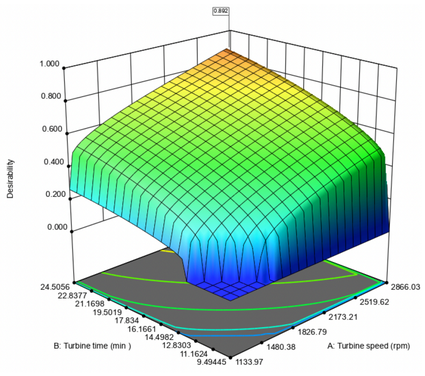

Figure 3: 3D surface of desirability with the flag on the solution with greater value.

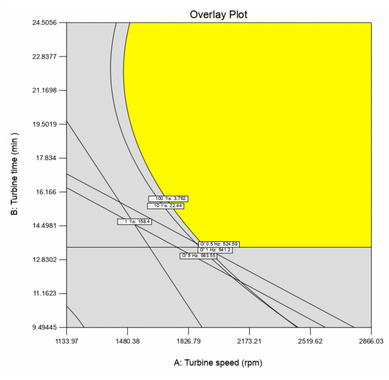

Figure 4: Overlay plot of DoE process parameters.

Design Space

The Design Space is defined as "the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality". [2]
As result of the DoE, a Design Space was defined for the manufacturing process.
In Figure 4, the highlighted area represents the space in which, at fixed planetary time during final mixing, is predicted to obtain a product of the desired quality, even variating the ideal setting of the other two process parameters (turbine time and speed during pH adjustment).

Updated Risk Assessment and Control Strategy

As result of the experimentation, the initial manufacturing process risk assessment was updated according to the gained process knowledge and understanding; the initially identified high risks variables were addressed and reduced to an acceptable level of risk. Moreover, the CQAs which were considered unlikely to be impacted by process variables and were not analyzed in detail during development, but still were QTPP target elements, were included as part of the control strategy, which is defined as "a planned set of controls, derived from current product and process understanding, that assures process performance and product quality". [4]

Table 4: Final risk assessment of the manufacturing process for generic Adapalene 0.1% gel.

Drug Product CQAs	Process step				
	Polymer hydration	API dispersion	Preliminary Mixing	Polymer neutralization	
	Carbopol dispersion	API wetting	Preliminary Mixing	pH adjustment	Final Mixing
Particle size distribution	Low	Low	Low	Low	Low
Rheological properties	Low	Low	Low	Low	Low
API Assay	Low	Low	Low	Low	Low
pH	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low

Conclusions

The application of QbD in pharmaceutical manufacturing has become an essential approach for the pharmaceutical industry to ensure the efficacy and safety of pharmaceutical products. Therefore, manufacturers need to consider employing QbD to identify and classify product attributes as well as material/process parameters with a deeper understanding of their complex interplay using proper experimental design and statistical analysis. QbD implementation is vital to ensure the final product attributes and the intended therapeutic and safety profiles. [5]

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[2] ICH Harmonised Tripartite Guideline: Q8 Pharmaceutical Development. August 2009.
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