



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<10th October 2014>

Submission of comments on '< [Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission](#) >' (EMA/ CHMP/BWP/187338/2014)

Comments from:

Name of organisation or individual

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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).



1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>	<p>Thermal Analysis is considered as one of the most popular techniques in material sciences and engineering. Thermal Analysis is a highly sensitive method to study the thermotropic properties of many different macromolecules (i.e. proteins, lipids, etc). This gamut of techniques has been applied to the pharmaceutical field with studies of excipients, biomaterials, nanomaterials and active pharmaceutical ingredients. Applications of this technique to biotechnological products include the measurement of their thermodynamic parameters and a detailed characterization of thermotropic and phase transition behavior. Advanced technologies connect physicochemical characteristics (polymorphism, fluidity, surface charge etc.) with the alteration of pharmacokinetics, biodistribution profile of drugs and thus reduction of the side effects. As formulations become more and more complex and characterizing them becomes more difficult, manufacturers have done an excellent work in keeping pace with more precise and sensitive yet more durable instruments. Thermal analysis casts light in a total new scientific perspective by facing drugs as biomaterials and not as plain materials. In the pharmaceutical sciences, only a handful of the techniques are commonly employed but the information gained and phenomena, like aggregation, that can be explored are countless</p>	<i>(To be completed by the Agency)</i>

2. Specific comments on text

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
191-195		<p>Comment: Proteins are characterized by dynamics and flexibility. There is interplay between the structure and the dynamics of biomaterials (i.e. proteins etc.). Thermal analysis techniques can provide their thermodynamic signature and quantify their biophysical behaviour.</p> <p>Proposed change (if any): These activities could include evaluation of specific cell traits or indices (e.g. morphological characteristics, growth characteristics (population doubling level), cell number, viability, biochemical markers and their biophysical behaviour, immunological markers, productivity of the desired product, oxygen or glucose consumption rates, ammonia or lactate production rates), process parameters and operating conditions (e.g. time, temperatures, agitation rates, working volumes, media feed, induction of production).</p>	
246-248		<p>Comment: The morphology and the shape, as well as the shape/morphology balance of biomaterials are directly related to their colloidal and biological behaviour. From the pharmaceutical point of view, thermal techniques are used in order to evaluate the physicochemical properties of drugs and their interactions in biological level, as well as their behaviour during the formulation process.</p> <p>Proposed change (if any): This generally includes establishment of adequate analytical methods (including</p>	

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		<p>thermal analysis techniques) required for their detection and an estimation of the concentrating or removing capacity for each unit operation followed by the determination of appropriate acceptance criteria (based on morphological and thermotropic criteria).</p>	
290-291		<p>Comment: The simple thermal analysis experiments provide insight into complex biological problems guide and drive new directions in evaluation of biotechnological products.</p> <p>Proposed change (if any): Studies via thermo-analytical techniques conducted under worst case conditions and/or abnormal conditions (e.g. higher temperature, longer time) could be used to further support the suitability of the claimed conditions.</p>	

Please add more rows if needed.