# Generics – An MCC perspective

# Overview

- Medicine Registration
- Regulatory burden and knowledge
- Essential Similarity
- Mechanisms to reduce regulatory burden
  - Harmonisation
  - Processes
  - Memberships
- Why dissolution in support of efficacy/safety?
- Conclusion

# Medicine Registration

- Objective
  - Ensure  Quality Safe and Effective Medicines

# Medicine Registration

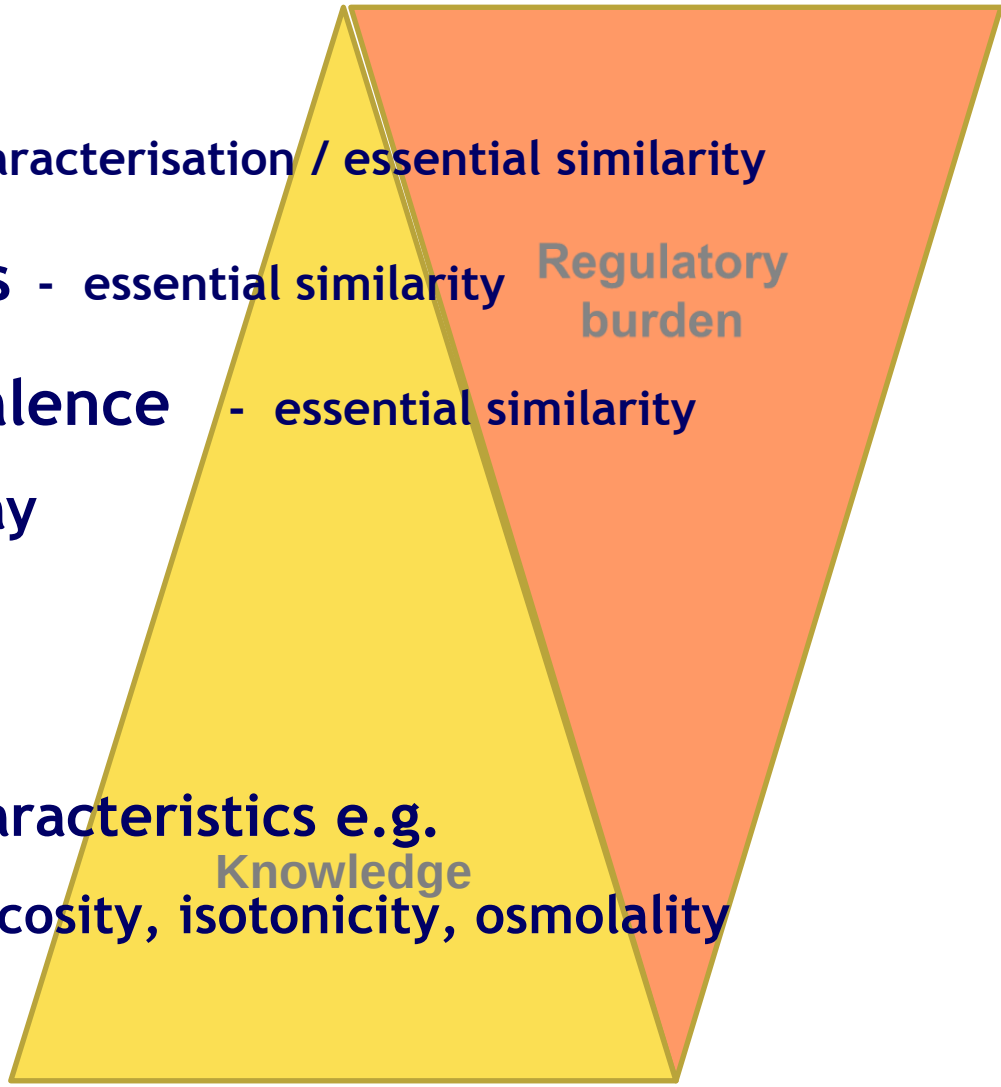
- Applicant to demonstrate ability to Consistently produce quality, safe, fit for intended use medicines
  - Demonstrate quality, safety and efficacy - product dossier
  - being in control of quality management system, and
  - operation at acceptable levels of compliance with principles and guidelines of cGMP

# Medicine Registration

- Objective
  - Ensure  Quality, Safe and Effective (qse) Medicines
  - **Promote access to affordable, quality medicines**
    - **Generic / Interchangeable medicines -**
      - **safety and efficacy outcomes of NCE maintained over life cycle irrespective  of manufacturer**
      - **approved dose range, package insert- similar/same dosage and directions for administration +**
      - **comparable quality**
    - **Reduce regulatory burden but maintain qse**

# Efficacy *and* Safety

- Clinical trials — characterisation / essential similarity
- Bioequivalence studies - essential similarity
- Pharmaceutical equivalence - essential similarity
  - API strength and assay
  - Formulation
  - Impurity profile
  - Physico-chemical characteristics e.g.
    - Dissolution, pH, viscosity, isotonicity, osmolality



# Safety & Efficacy *contd*

PA CTD gdl 3.2.R.1 II (1)

- High level of assurance
  - trial or study batch(es) representative of marketed batches
  - product and process used in the production of the product will be feasible on an industrial scale
- Measure of assurance ensured by
  - appropriate final product specifications
  - demonstration of essential similarity

# Essential similarity (ES)

Biostudies gdl 4

It is incumbent upon the applicant to demonstrate in the dossier (not in the BE report) that the

- excipients in the pharmaceutically equivalent product are
- essentially the same and in
- comparable concentrations as those in the reference product.

In the event that this information about the reference product cannot be provided by the applicant, it is incumbent upon the applicant to perform *in vivo* or *in vitro* studies to demonstrate that the differences in excipients do not affect product performance.

# ES *contd*

Biostudies gdl 4.3

- Aqueous solutions to be administered by parenteral routes (IV, IM, SC) containing the same API(s) in the same molar concentration and the same or similar excipients in comparable concentrations as the comparator product are considered to be equivalent without the need for further documentation, *other than the comparison between test and reference*.

- Certain excipients
(e.g. buffer, preservative, antioxidant) may be different provided the change in these excipients is not expected to affect the safety and/or efficacy of the medicine product.

# ES *contd*

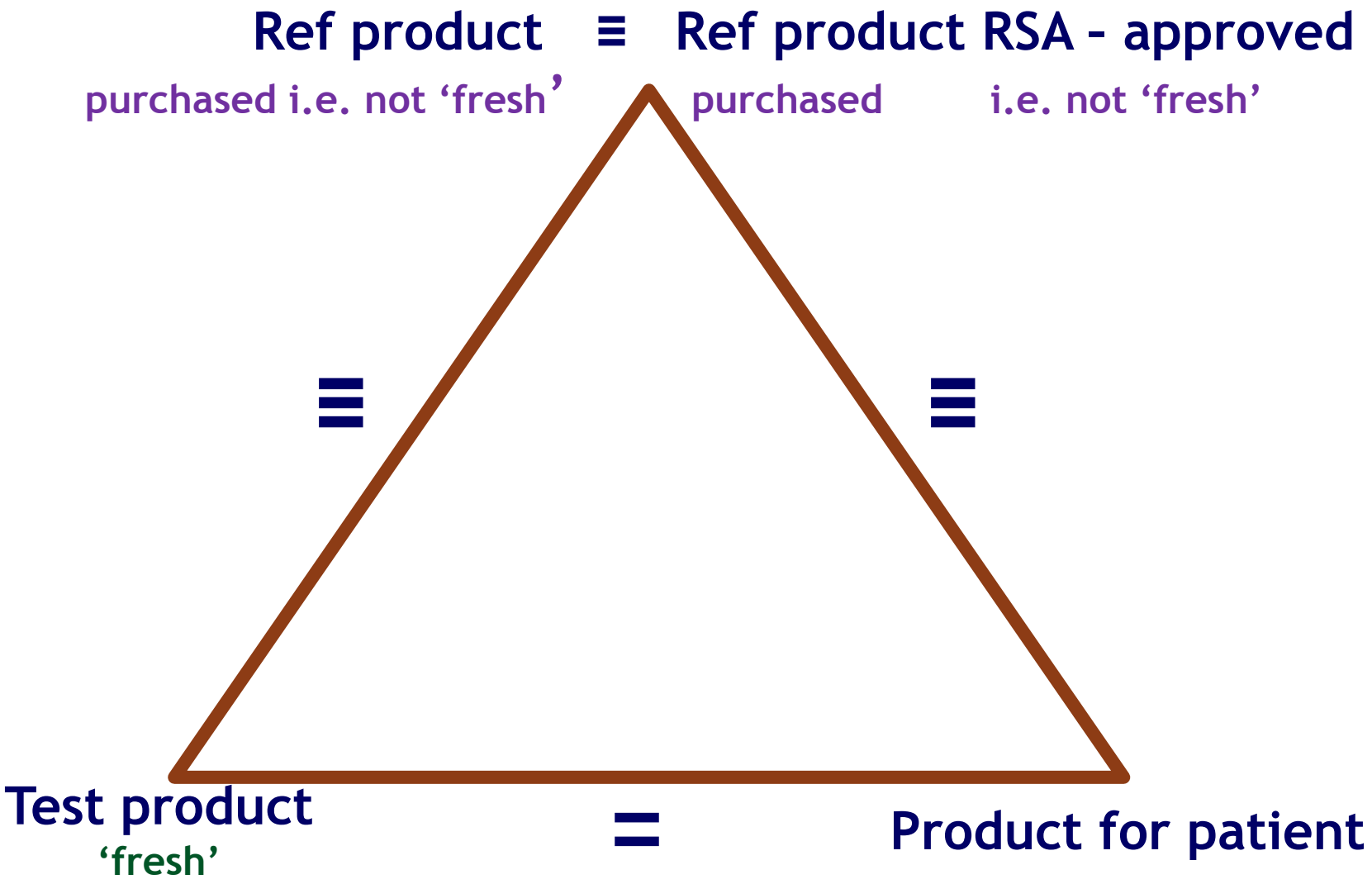
PA CTD gdl 3.2.R.1 I (iii)

- **No data presumed required to substantiate efficacy**

  (e.g. parenteral solutions)

  - **clearly state rationale for accepting safety and efficacy &**
  - **include a discussion on the excipients (Biostudies gdl section 4), &**
  - **a comparison of final product characteristics (in 32R142)**

# ES


Ref product ≡ Ref product RSA - approved PI
purchased i.e. not 'fresh'
purchased
i.e. not 'fresh'
≡
≡
Test product
'fresh'
=
Product for patient

# ES products

- Effects of dosage form/formulation parameters with respect to
  efficacy and safety *as well as quality*
  can be expected to be essentially the same

- Pharmaceutically equivalent (PE) or alternative (PA)
  - Dose; Dosage form; Same moiety salt, ester

    ***Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ either in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength, administered by the same route of administration but are otherwise not pharmaceutically equivalent.***

- PE or PA not necessarily ES
- PE or PA + similar Quality ≡ ES

# ES Parameters

*Reference product supported by clinical*

PA CTD 32P51 (5)
P&A gdl 3.6.5

Stability gdl 1.1.1 d)

Biostudies gdl 4

- Parameters common to all dosage forms
  - Assay lower limit at least 95 % (*'fresh' vs 'not fresh'*)
  - Impurity profile specifications representative of reference products supporting the clinical data base, and the test
  - Formulation
- Parameters dependent on dosage form *and* intended site of administration
  - Non solns: (Solid oral/semisolid topical) Dissoln profiles
  - Solns: Isotonicity; osmolality; pH; density; viscosity; buffers

# Mechanisms ↓ regulatory burden

- Harmonisation of Requirements
- Processes
- Memberships

# Mechanisms ↓ regulatory burden

- **Harmonisation of Requirements**
  - Quality, safety, efficacy and GMP
  - ICH, FDA, EMA, WHO, PIC/S
  - API : CEP, WHO Pre Qualification
- **Guidelines**
  - Labelling
  - Pharmaceutical and Analytical / PA CTD guidelines
    - API DMF
  - Stability
  - Dissolution
  - Biostudies
    - Food effect
    - Biowaivers
  - Amendments
    - API

# Mechanisms ↓ regulatory burden

- **Processes**
  - Application form: MBR1 to MRF1 to CTD
  - eCTD
  - Multiple applications of the same product
  - EDMS

- **Memberships**
  - PIC/S
    - Harmonisation of GMP requirements - Reduction of inspections
  - WHO / ICDRA
    - promoting exchange of information and collaborative approaches to issues of common concern authorities in their efforts to harmonize regulation and improve the safety, efficacy and quality of medicines.
  - IGDRP - Int Generic Drug Regulators Pilot
  - Other

# IGDRP (Int Generic Drug Regulators Pilot)

- **Introduction**
  - Increasing no of generic applications – significant pressures on authorities, increasing workload, global production and distribution
- **Need for regulatory cooperation and convergence**
  - Regulatory convergence: process of alignment of regulatory requirements and approaches as harmonized technical guidelines, standards and scientific principles are adopted and similar regulatory practices and procedures are introduced
  - Regulatory convergence: makes cooperation and collaboration between regulatory authorities possible
- **Meetings of regulators**
  - Ottawa October 2011; Washington April 2012; Nanchang Dec 2012; Canberra May 2013; Geneva Oct 2013; Chinese Taipei May 2014; Singapore November 2014
- **Scope**
  - Activities with focus on premarket review of generics - NOT biosimilars

# IGDRP *contd*

- **Mission**
  - Promote collaboration and convergence in generic regulatory programmes to address challenges posed by increasing workloads, globalization and complexity of scientific issues
- **Key operating principles**
  - Decision-making by consensus - "opt-out" option
  - Activities to complement and not duplicate work undertaken elsewhere
- **Diversity - requirements & capacity of IGDRP regulators**
  - Working definition for Generic
    - A generic drug is generally defined as a drug product that is equivalent to a reference product in active pharmaceutical ingredient, dosage form, strength, route of administration, quality and performance characteristics and intended use
- **Progress**
  - Gap-analysis of regulatory requirements and approaches
  - Survey on laws, policies and procedures re management and sharing of non-public information
  - Electronic platform for the sharing of non-confidential information

# IGDRP *contd*

- **Members**
  - Australia, Brazil, Canada, China, the European Union, Japan, Korea, Mexico, New Zealand, Singapore, South Africa, Switzerland, Taiwan as well as the European Directorate for the Quality of Medicines and Healthcare (EDQM) and the World Health Organisation
- **Work areas**
  - **Work sharing** – manner similar to the European Decentralised/ Mutual Recognition procedures
  - Active Substance Master Files (ASMF) / Drug Master files (DMFs) - work sharing not possible for SA – only open part DMF
    - Quality assessment template
  - Biowaivers - work sharing not possible – all that accept BCS require local ref
    - BCS Biowaiver evaluation template, list of BCS I candidates in progress
- **Industry support**

# Why dissolution?

## Clinical effect prerequisite

- Availability of active / release of the active from the dosage form
- Delivery of the active moiety in solution to the site of action
- Absorption
- Permeation
- Elimination

# Solid oral dosage forms

- Chain of events:
  - Disintegration
  - Dissolution

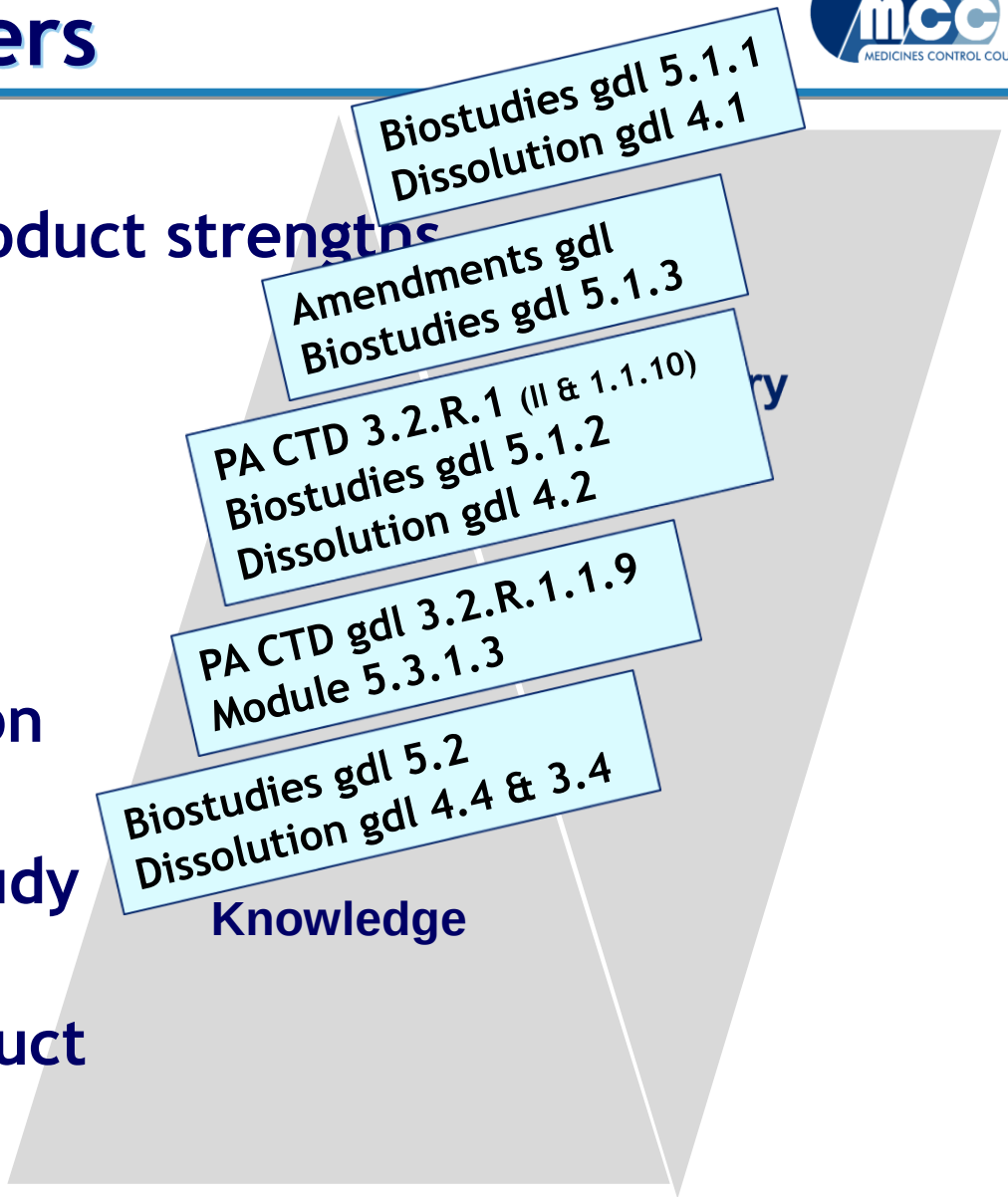
  } true solution, - formulation effects (control of manufacturer)

  - Absorption
  - Permeation

  } Absorptive & metabolic pathways of individual (beyond control of manufacturer)

# Dissolution Biowaivers

- Proportionally similar product strengths
- Amendments
- Reference products
- *In vivo in vitro* correlation
- BCS biowaiver - no biostudy
- Optimal performing product



# BCS - Risk Management Tool

- BCS is a scientific framework for classifying APIs and identifying low-risk products based on three major factors their
  - solubility, and
  - intestinal permeability (absorption)
  - and dissolution

  that govern the rate and extent of absorption from IR solid oral dosage forms

Biostudies gdl 5.2
Dissolution gdl 4.4

- HS/HP/RD to minimize the risks associated for decisions on biowaivers

Dr V Shah SIRHS 2005

# BCS-based Biowaiver

- An approach to reduce *in vivo* bioequivalence studies
- *In vivo* BE studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by *in vitro* data
- Restricted to highly soluble APIs
  - with known human absorption
  - not considered to have NTI
  - IR, solid dosage forms for oral administration and systemic action - same dosage form
    - Excluding sublingual, buccal & MR formulations
    - Orodispersible formulation when absorption in oral cavity can be excluded

Biostudies gdl 5.2

# BCS-based Biowaiver

- Intended to address bioequivalence between specific test and reference products

Biostudies gdl 5.2

- Principles applicable for :
  - Clinical trial products and to-be marketed products
  - Innovator product line extensions,
  - Generic medicines,
  - Amendments/variations that require proof of efficacy (BE studies)

# BCS Class I Biowaiver

Biostudies gdl 5.2
Dissolution gdl 4.4

## Applicable *if*

- API proven to have high solubility and complete absorption  BCS Class I, ***and***
- Either very rapid (>85 % at 15 min) or similarly rapid (85 % at 30 min) dissolution of test & reference products, ***and***
- IPIs that might affect bioavailability* are
  - identified  and possible impact addressed
  - are qualitatively and quantitatively the same. Generally same IPIs in similar quantities preferable

# BCS class III Biowaiver

## Applicable *if*

Biostudies gdl 5.2

- API proven to have high solubility and limited absorption  BCS Class III, ***and***
- Very rapid (>85 % at 15 min) dissolution of test and reference products in specific media, ***and***
- IPIs that might affect bioavailability* are
  - identified  and possible impact addressed
  - are qualitatively and quantitatively the same. Other IPIs the same and in similar quantities

# BCS Class I & III Biowaivers

- IPIs
  - state function/purpose
  - consider & discuss possible interactions affecting bioavailability and solubility
  - justify quantity within normal range

Biostudies gdl 5.2.3

- Identify *IPIs that might affect bioavailability
  - e.g. sorbitol, mannitol, SLS, other surfactants; and also their possible impact on
    - GIT motility
    - Susceptibility of interactions with API (e.g. complexation)
    - API permeability
    - Interaction with membrane transporters

# Optimum Product Performance

- USP Medicine Compendium (MC) ingredient and product monographs outside USA
- General Chapter 12 extends BCS approach, in certain cases eliminating need for comparison studies
- Dissolution event occurs in region of the GI tract that provides a pH at which API is soluble and where absorption can occur

Shah VP, Cecil TL, Srinivasan SV, Williams RL. Progressively Reducing Regulatory Burden. *The AAPS Journal, Vol 16, No 4 July 2014*

# Optimum Product Performance

- Two dissolution media:  pH 1,2 buffer pH 6,8
  - Basket 100 rpm paddle 50 rpm
- Highly soluble API - highest dose in 250 ml
- Very rapid/Rapid dissolving final product
  - Soluble in both then pH 1,2 85 % (Q) in30 min
  - Soluble in pH 1,2 only then 85 % (Q) in15 min + pH 6,8 t=r
  - Soluble in pH 6,8 only then 85 % (Q)  in 15 min

Shah VP, Cecil TL,  Srinivasan SV, Williams RL.  Progressively Reducing Regulatory Burden. *The AAPS Journal, Vol 16, No 4 July 2014*

# Topical dosage forms - semisolids

- Dissolution  similarly recognized
  - by US FDA's SUPAC-SS after certain manufacturing changes

  - Qualitative formulation (Q1)
  - Quantitative formulation (Q2)
  - Same release characteristics (Q3)

Shah VP, Cecil TL,  Srinivasan SV, Williams RL.  Progressively Reducing Regulatory Burden. *The AAPS Journal, Vol 16, No 4 July 2014*

# Conclusion - *Consider*

- Reference product characteristics
  - Dosage regimen, food effect
  - Quality
- Clinical/BE test product quality characteristics
- Specifications appropriate?
  - Assay
  - Impurity profile
  - Release of active
  - Physico-chemical characteristics
- Will the marketed product be ES to Reference prod & Product as applied for?

# Conclusion - ⬇ *Regulatory burden*

- Increased Responsibility
  - Applicant
    - All departs incl Regulatory personnel
  - Authority
    - Reviewer
    - Secretariat