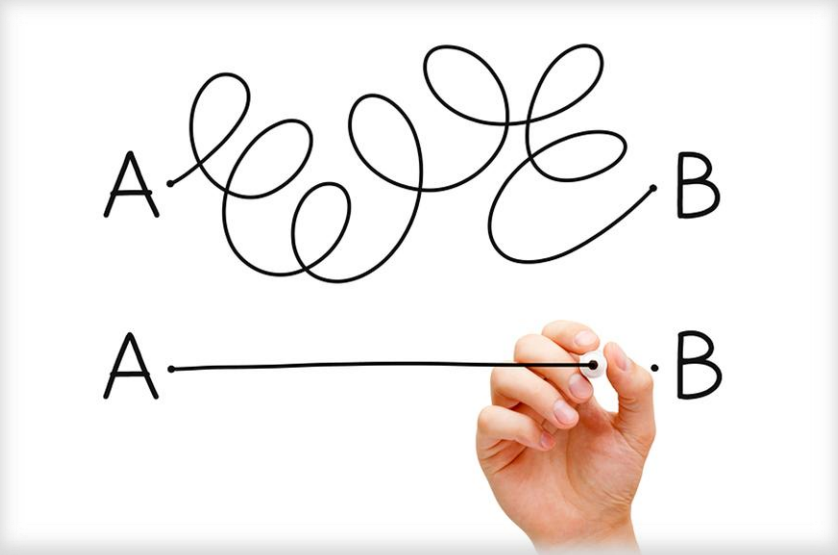
GLOBAL VIEW ON REGULATORY AFFAIRS



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25th Feb 2021

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A new way for a new world

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Global Regulatory Affairs – Simple or Complex??

Few critical challenges faced by the Industry which requires steps towards Harmonization:

1. Faced paced actions of FDA and the anticipated actions on product extensions – Complexity of COPPs
2. Nitrosamine Risk assessment and vendor support
3. Compendia Harmonization Challenges
4. Data and Reference product requirements in harmonized product development
5. Complex Generics and Paradigm shift on the requirement of Q1+Q2 and Now Q3 Similarity
6. IIG Evaluation and potential RTR concerns
7. RLD labelling updates and its impact on timely ANDA approval

Regulatory Harmonization – Need of the Hour

U.S. FOOD & DRUG ADMINISTRATION

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Australian Government
Department of Health
Therapeutic Goods Administration

MHRA
Regulating Medicines and Medical Devices

HSA
Health Sciences Authority

MoH - Russia

Health Canada

ANVISA
Agência Nacional de Vigilância Sanitária

Republic of the Philippines
Department of Health
Kagawaran ng Kalusugan

Pmda 独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

APIC active pharmaceutical ingredients committee
25 years of promoting patient safety

ICH
harmonisation for better health

Image Credit: www.fdli.org

IPA
Innovation, Quality and Global Reach

IPEC FEDERATION

World Health Organization

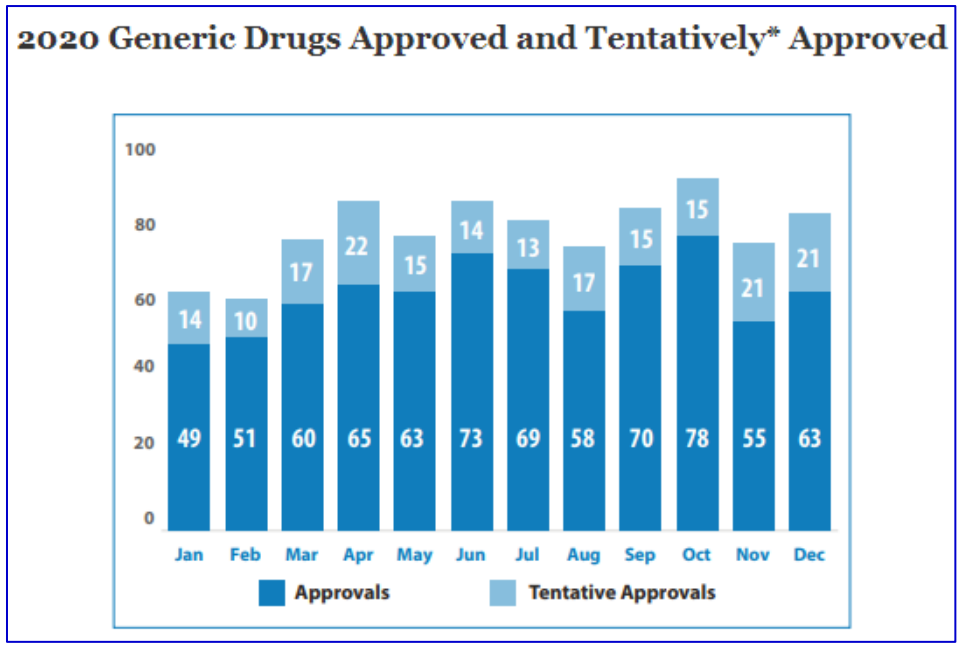
Fast paced actions from US FDA during COVID & Anticipated impact on Product Extensions

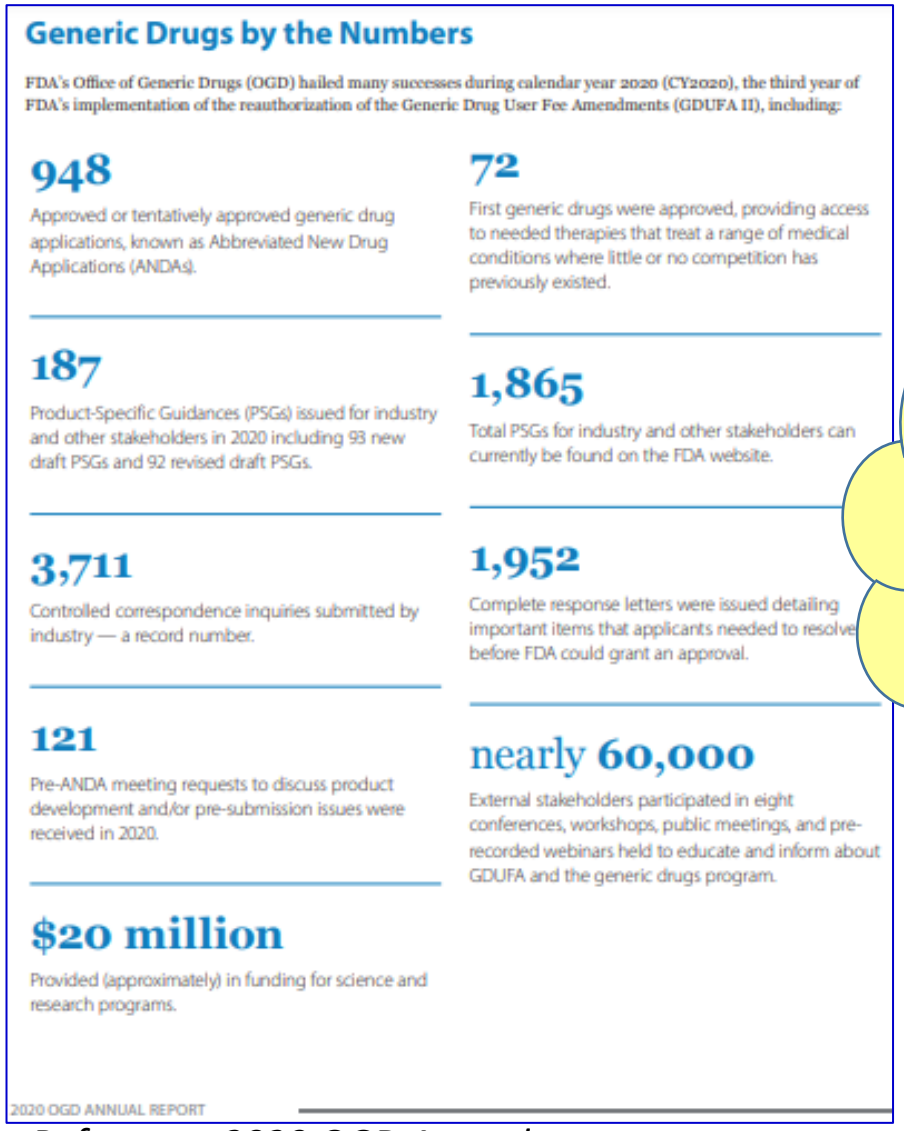
Approvals / Tentative Approvals – 948 ANDAs

- Includes 72 1st time *gRx*
- 35 *gRx* with CGT Designation (17 CGT Approvals if Q1 FY 2020)

Responded to 3,711 Controlled Correspondences

121 Requests for product development and pre-ANDA meetings





Translates to more anticipated product extensions based on CPP to other markets who are not so fast paced

Reference: 2020 OGD Annual report

Certificate of Pharmaceutical Product- CPP

Emerging Market Health Authorities – CPP Expectation

Product to be approved and being commercial in the country of origin (where the product is manufactured)

Definition of CPP –

Certificate for a Pharmaceutical Product is an evidence of GMP, Quality, Safety, Efficacy review and approval by a competent Health Authority.

When would a CPP be required

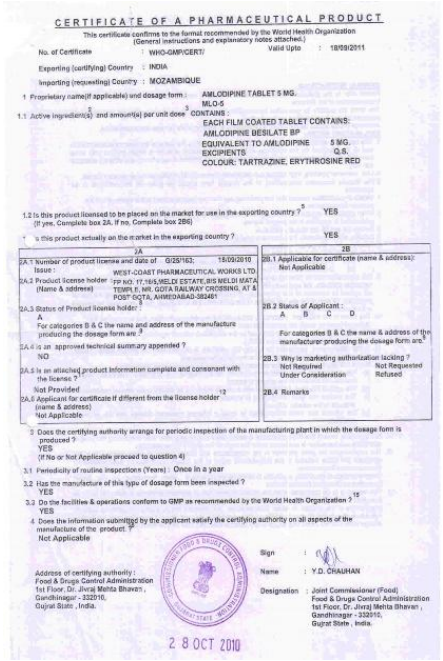
- A recipient authority could require a CPP when it does not undertake a full review of QSE data submitted for registration

Is it possible to obtain a CPP from a certifying authority that is not the country where the manufacture of the finished product takes place?

- Yes, the GMP declaration in the CPP will refer to assurance of GMP for the product approved in the certifying country at the stated site, even if the manufacturing site is in a different country than the issuing authority

Is it necessary for the CPP to come from the country where the Finished product manufacture takes place

- No, although the Scheme was set up assuming that the certifying country was also the country where finished product manufacture takes place, there is scope within the Scheme for CPPs to be issued by other authorities that can provide independent assurance of the GMP compliance status



CERTIFICATE OF A PHARMACEUTICAL PRODUCT

This certificate confirms to the format recommended by the World Health Organization (General instructions and explanatory notes attached.)

No. of Certificate : WHO-GMP/CERT/ Valid Upto : 18/09/2011

Exporting (certifying) Country : INDIA

Importing (requesting) Country : MOZAMBIQUE

1 Proprietary name(if applicable) and dosage form : AMLODIPINE TABLET 5 MG. MLO-5

1.1 Active ingredient(s) and amount(s) per unit dose CONTAINS : EACH FILM COATED TABLET CONTAINS: AMLODIPINE BESILATE BP EQUIVALENT TO AMLODIPINE 5 MG. EXCIPIENTS Q.S. COLOUR: TARTRAZINE, ERYTHROSINE RED

1.2 Is this product licensed to be placed on the market for use in the exporting country ? YES (If yes, Complete box 2A. If no, Complete box 2B6)

1.3 Is this product actually on the market in the exporting country ? YES

2A

2A.1 Number of product license and date of Issue : GI/25/163; 18/09/2010 WEST-COAST PHARMACEUTICAL WORKS LTD.

2A.2 Product license holder (Name & address) SURVEY NO. 17, HAJIMELDI ESTATE,B/S MELDI MATA TEMPLE, NR. GOTA RAILWAY CROSSING, AT & POST GOTA, AHMEDABAD-382481

2A.3 Status of Product license holder : A For categories B & C the name and address of the manufacturer producing the dosage form are :

2A.4 Is an approved technical summary appended ? NO

2A.5 Is an attached product information complete and consonant with the licence ? Not Provided

2A.6 Applicant for certificate if different from the license holder (name & address) : Not Applicable

2B

2B.1 Applicable for certificate (name & address): Not Applicable

2B.2 Status of Applicant : A B C D For categories B & C the name & address of the manufacturer producing the dosage form are :

2B.3 Why is marketing authorization lacking ? Not Required Not Requested Under Consideration Refused

2B.4 Remarks

3 Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced ? YES (If No or Not Applicable proceed to question 4)

3.1 Periodicity of routine inspections (Years) : Once in a year

3.2 Has the manufacture of this type of dosage form been inspected ? YES

3.3 Do the facilities & operations conform to GMP as recommended by the World Health Organization ? YES

4 Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product ? Not Applicable

Address of certifying authority : Food & Drugs Control Administration 1st Floor, Dr. Jivraj Mehta Bhavan , Gandhinagar - 382010, Gujrat State , India.

Sign :

Name : Y.D. CHAUHAN

Designation : Joint Commissioner (Food) Food & Drugs Control Administration 1st Floor, Dr. Jivraj Mehta Bhavan , Gandhinagar - 382010, Gujrat State , India.

28 OCT 2010

Working document QAS/10.374- WHO CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE: Questions and answers (Q & A)

Certificate of Pharmaceutical Product- CPP

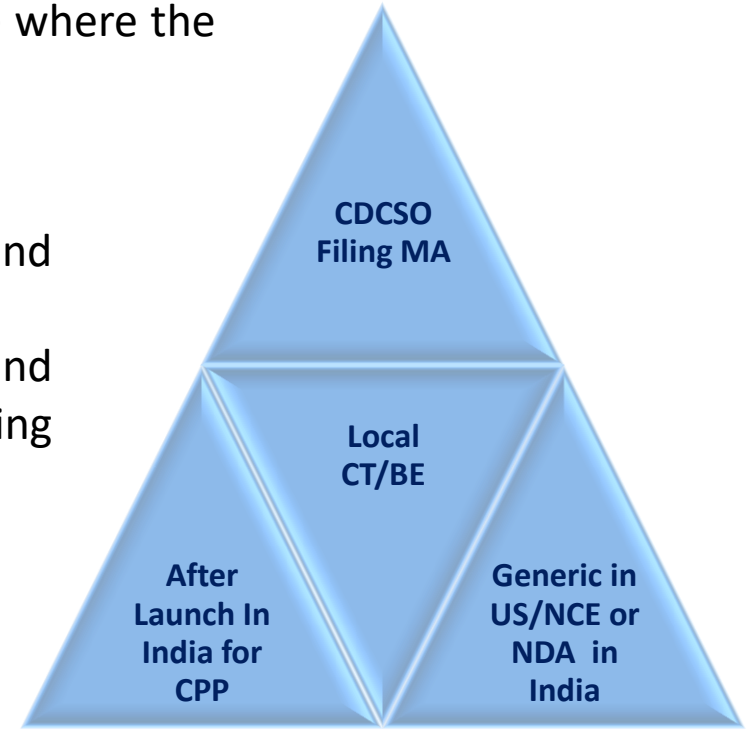
WHO –

1. If the CPP is made available from a competent authority (High surveillance) then the Importing Country Health Authority **need not undertake a full review of QSE** data submitted for registration
2. Proof of **GMP compliance** for the site where the product is manufactured

Health Authorities –

1.Proof that the product is approved and commercial

2.The product is actually consumed and safe in the Population of the exporting country where it is manufactured



Complex process to get CPP for the products which are US/EU extensions to Emerging markets/NCE/NDA in India

Certificate of Pharmaceutical Product- CPP

1.2

- Is this product licensed to be placed on the market for use in the exporting country? (Yes/No)

1.3

- Is this product actually on the market in the exporting country? (Yes/No)

1.2 &1.3 Yes	1.2 & 1.3 Yes/ No	1.2 & 1.3 No/ No
• Argentina, Mexico • Colombia, Peru • Ecuador, Malaysia • Philippines, Vietnam • Myanmar , Kazakhstan • UAE , Thailand • Singapore, Indonesia • Cambodia, Sri Lanka • Taiwan, Dominican Republic • Jamaica , Egypt , Iraq	• Brazil • Hong Kong • Laos • Tanzania • Maldives	• Russia • Ukraine • Kenya • Georgia • Belarus • Azerbaijan

Nitrosamine Risk Assessment

N-Impurity	USFDA	EMEA	Health Canada
NDMA	√	√	√
NDEA	√	√	√
NMBA	√	√	√
NIPEA	√	√	√
NDIPA	√	√	√
NDBA	√	√	√
NMPA	√*	√*	√*
MeNP (1-methyl-4-nitrosopiperazine)	-	-	√*
Timeline for Risk Assessment	March 01, 2021	March 31, 2021	March 31, 2021
Timeline for Confirmatory testing	ASAP	ASAP	October 1, 2022
Changes to MA	3 Years from Guidance (Sept '23)	September 26, 2022	October 1, 2022

Safety

v/s

Affordability

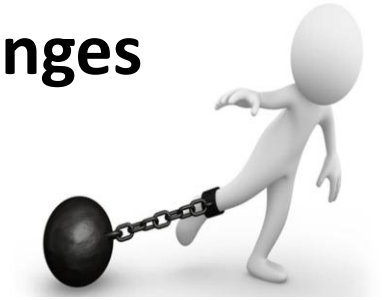
Challenges

- Vendor Declarations
- Frequent updates in including more N-Imp
- Availability of method and CROs
- How much is adequate?
- Limits and Method sensitivity

*Frequent updates from various HA on additional known N-Imp as more and more information is shared with the Agencies is a challenge from both API Supplier's assessment as well as internal Risk Assessment by the MAH – **Scope of a Harmonized Approach***

**Included in latest published guideline*

Compendia Harmonization Challenges



Differences in the Pharmacopoeial standard preferences and specifications

EU and other regions viz. Russia/Ukraine/South Africa are more inclined towards.
BP and Ph. Eur
Where as **Latam/Asian** countries are towards – **USP standards**

Example – USP and Ph. Eur Monograph of Clobetasole Propionate -

British Pharmacopoeia

U.S. Pharmacopeia
The Standard of Quality℠

Clobetasole Propionate		USP	Ph Eur
Related substance			
	Betamethasone 17 propionate	Not listed	0.20%
	Clobetasol dalta 16	Not listed	0.30%
	1,2 dihydroclobetasol propionate	Not listed	0.20%
	21 chloro-16B-methyl 3,0 dioxopregn 1 - 4 diene -17 ylpropanoate	Not listed	0.30%
	Each unknown impurity	1.00%	0.10%
	Total impurities	2.50%	1.00%
SOR		+98^{0}C to 104^{0}C in Dioxane	+112^{0}C to +118^{0}C in Acetone
Loss on drying		NMT 2.00 %	NMT 0.5%

Leveraging Data from US/EU Development Program to Emerging Markets

Facility Audits – Health Authorities which do not recognize USFDA/PICS need Physical audits – ANVISA, SFDA (Saudi Arabia), Kenya and other African countries

OSDs- Dissolution Data

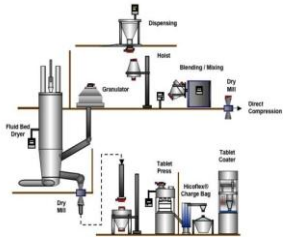
- Comparative Dissolution profile, Multi media against US and Local RLD
- Dissolution development report as OGD recommendations are used for US
- Dissolution media with Surfactant - US follows USP or OGD recommendation; whereas Emerging countries prefer to have dissolution profiling data without surfactant

Stability Studies –

- 3 batches – Zone IVB
- In-use – Considering the US market prefers Bottle/container packs

AMVs: Brazil Specific -

- Site AMVs API & FP with use of Pharma standards, Linearity in Triplicate etc.
- Forced Degradation to be part of Assay & Related Substances in API & FP AMVs (min 10-30% degradation or 10 days with Acid/Base/Heat/Light/ Oxidation/Humidity/Metal Ions to be performed & % degradation to be reported)



Process validation protocol and Report –
With Challenge studies – Initial application

Pre-clinical / Clinical

Overviews and Summaries, Module 4 and Module 5 as per ICH TOC

Acceptance of Global Reference Product for BE Studies






Russia	Brazil	Mexico	Malaysia Philippines Singapore	Thailand	Ukraine Colombia Peru Ecuador
☹	☹	☹	☺	☹	☺

Unique Country Specific Guidelines – Challenge in Global Harmonization

COUNTRY SPECIFIC GUIDELINES-

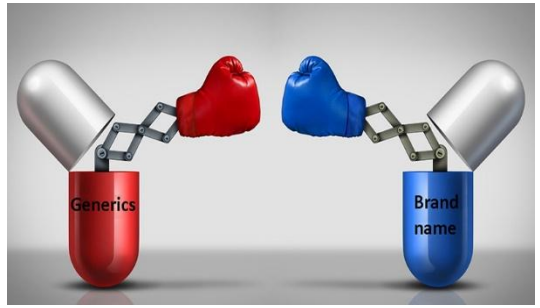
- **Russia** needs analytical methodologies as per Russian Pharmacopeias / EAEU methodologies.
- **Brazil** needs AMV's as per RDC 166, which needs repetition of most of the analytical parameters and Forced degradation using reference standards.
- Due to difference in local RLDs, need to generate the In-vitro data among the Global RLD and Local RLDs

PRIMARY PACK- Marketing need

For Emerging markets usually the necessity is of unit dosage ie Strip/blisters unlike that of US, where the preferred commercial pack is container.

LABELLING REQUIREMENTS – Branded or Generic

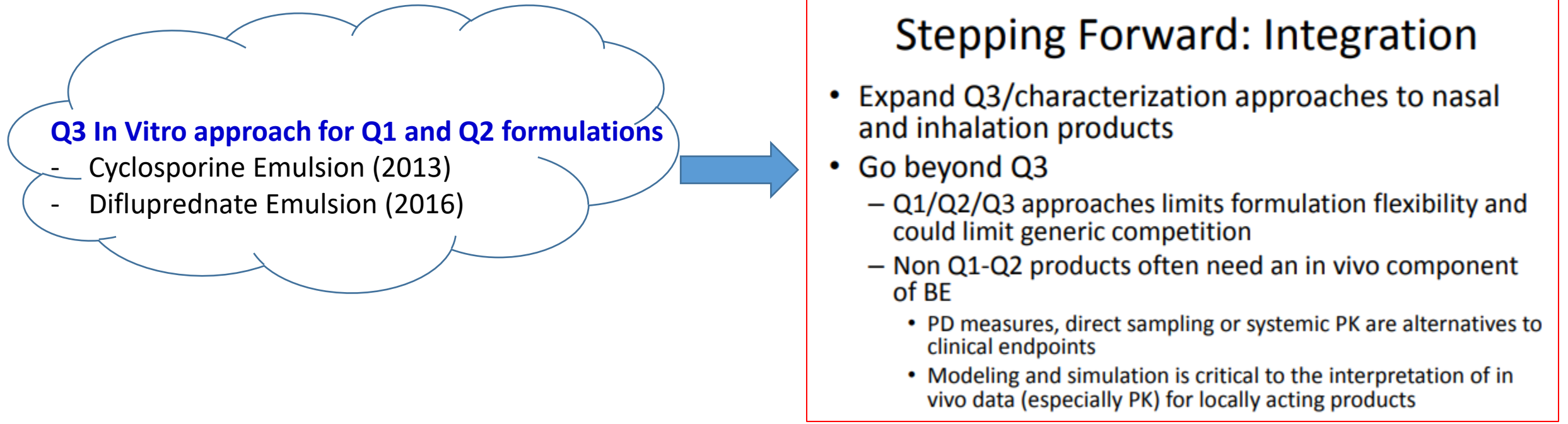
Emerging markets works on branded generics, hence each market has different trade names based on local trade mark clearance. Making it difficult to have same pack/brand across the globe.



Emerging requirements of Q1/Q2 and Q3 Similarity and going beyond…

Q3 In Vitro approach for Q1 and Q2 formulations

- Cyclosporine Emulsion (2013)
- Difluprednate Emulsion (2016)



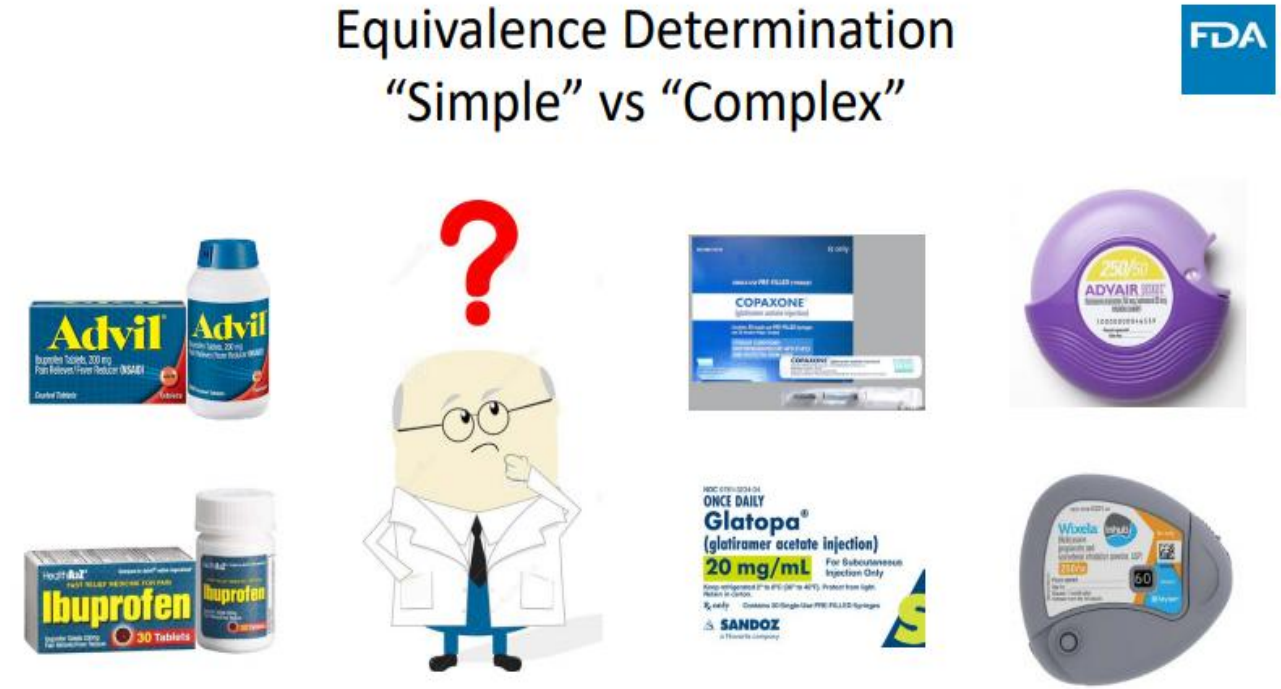
Reference: *Equivalence of Locally-Acting Drug Products: Markham C. Luke, May 3, 2017*

Other concerns – BE Guidance updates and RLD Updates

- GRx company followed the Product Specific guidance for a NTI with a passing BE study however during review phase the applicant had to re-perform the BE study in line with expectations of a NTI drug product
- Frequent or last minute RLD labeling updates has impacted many recent *gRx* approvals

Complex Generics

Traditional Generics
API Compendial requirements
Same Dosage Forms
PK Study for BE
Dissolution Similarity
Adequate Stability
Adequate Specifications
⇩
Faster APPROVAL



Reference: Overview of Complex Generics Regulatory Perspective on Bioequivalence; Xiaohui (Jeff) Jiang, PhD, *4th PQRI-FDA Conference on Advancing Product Quality; April 9 -11, 2019*

Complex Generics
API Characterization
Formulation Similarity
Clinical End Point studies
Device compliance
Complex Peptides
Advanced characterizations
Device Formulation interactions
⇩
Sluggish APPROVALs

Complex web of IIG Compliance

Route of Administration	Number of entries in IID
Oral	6395
Topical	1598
IV and IV (Infusion)	830
Ophthalmic	358
Vaginal	247
Subcutaneous	238
Transdermal	191
Nasal	155
IM	336
Sublingual	148
Rectal	137
Respiratory (Inhalation)	50
Others	1701
Total	**12384**

Concomitant Administration and cumulative levels of excipients

(glipizide)

10 mg

INACTIVE INGREDIENTS
Ingredient Name
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)
STEARIC ACID (UNII: 4ELV7Z65AP)

(atenolol)

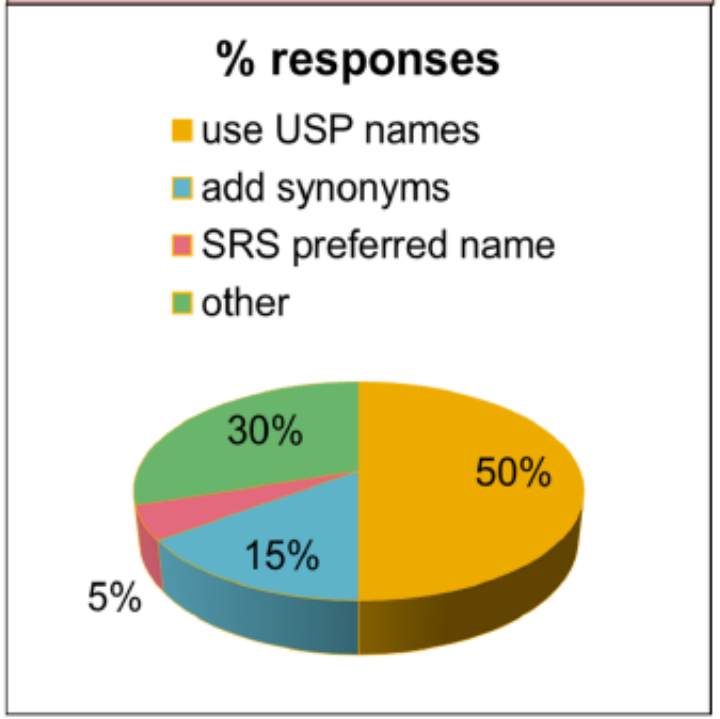
50 mg tablets

INACTIVE INGREDIENTS
Ingredient Name
MAGNESIUM STEARATE (UNII: 70097M6I30)
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)

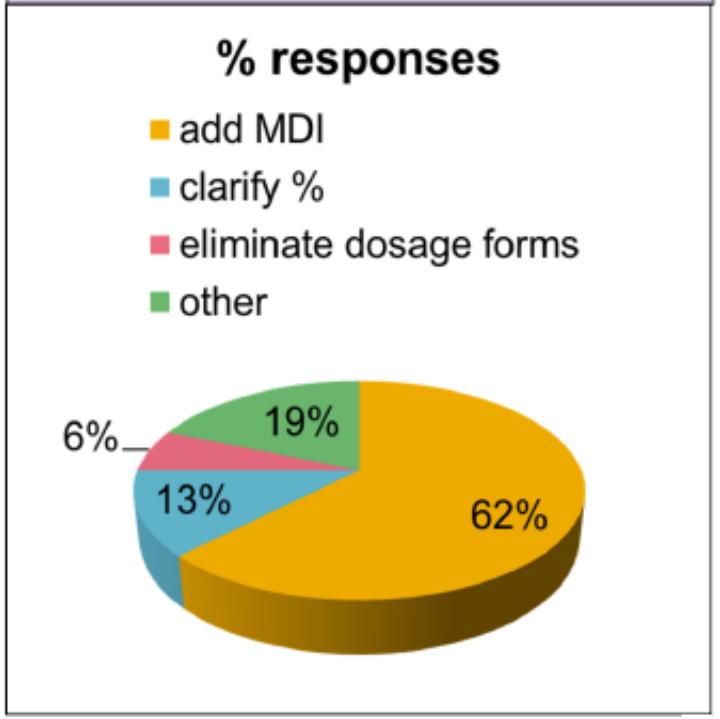
INACTIVE INGREDIENTS
Ingredient Name
D&C RED NO. 30 (UNII: 2S42T2808B)
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)
MAGNESIUM STEARATE (UNII: 70097M6I30)
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)
PEPPERMINT (UNII: V95R5KMY2B)
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)

Soliciting inputs from stakeholders

- How can we improve nomenclature?



- How should we identify excipient amounts?



IIG and Excipients Levels – What's acceptable and what's not? Needs intervention from Industry associations…

Safety v/s Affordability

Reference: ***Current FDA Perspective on Excipients, NJPhAST Meeting – September 15, 2016,*** *Jeffrey B. Medwid, Ph.D*

Key Take Away's:

- Industry and Health Authorities need to work more closely then ever in the current scenario to bring in Harmonization in all aspects of product life cycle and thereby ensure accessibility to quality affordable medicines across the markets
- Balance needs to be maintained in ensuring safety as well as affordability
- Harmonization efforts focused on aligning various compendial monographs
- Harmonized common template for Nitrosamine Risk assessment would bring in more uniformity in risk assessment
- ICH / WHO etc. needs to bring in more aspects of drug product development under their ambit as a baseline requirement across geographies.
- Initiatives from ICH/WHO/Industry association in bringing out guidance documents on issues such as product extensions leveraging CoPPs would bring in more predictability in quick availability of Complex drug products to Emerging Markets

Thank You

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