PRODUCT SPECIFIC GUIDANCE/GUIDELINES (PSG)

Loice Kikwai
Consultant
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INTRODUCTION

- Overview of EMA PSG
- Overview of US FDA PSG

EMA – CONCEPT PAPER (JULY – SEPTEMBER 2013)

- **Problem statement:**
- To further develop the **regulatory framework for demonstration of bioequivalence,** it is considered valuable to develop product-specific guidance based on the general principles. This should facilitate **transparent, predictable and scientifically robust assessment** in future marketing authorisation procedure
- The aim of developing such guidance is to **enable a consistent approach** to the assessment of applications **based on bioequivalence data,** particularly generic applications, across all submission routes.

EMA - PSG

- Give specific advice on **how bioequivalence should be demonstrated** to support **scientific consistency in their conduct and assessment.**
- Guidance on **generating relevant data** and potentially **improving the number of successful and well-conducted bioequivalence studies.**
- Allow for **timely and specifically guided generic drug development** with a standardized bioequivalence study design, which can thereby enable the **availability of generic medicinal products.**

- Website: 68 Finalized PSG's and 5 draft PSG's

EMA PSG

- Classification according to the Biopharmaceutical Classification Scheme (BCS) if a BCS biowaiver seems possible.
- Design elements of a bioequivalence study,
  - i.e. administration schedule,
  - study participants,
  - conditions for administration (fasting/fed),
  - strength to be investigated, and
  - number of studies.

EMA PSG

- Analyte for the bioequivalence demonstration,
  - i.e. parent/metabolite,
  - compartment (plasma/blood/urine), and
  - need for an enantioselective method.
- Criteria for bioequivalence assessment,
  - i.e. main pharmacokinetic variables and
  - width of confidence intervals.

EMA PSG

Overview of the European Medicines Agency's Development of Product-Specific Bioequivalence Guidelines

Jane O' Sullivan[1], Kevin Blake[1], Michael Berntgen[1], Tomas Salmonson[2] and Jan Welink[3]
on behalf of the Pharmacokinetics Working Party

- Does not:
- outline a waiver request of in vivo testing and the dissolution test method and sampling times required
- require the parent and the active metabolite to be analytically measured, only requires data on the parent compound
- separate guidance for specific dosage forms

IBUPROFEN ORAL USE IMMEDIATE RELEASE FORMULATIONS 200 - 800 MG PRODUCT-SPECIFIC BIOEQUIVALENCE GUIDANCE

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Ibuprofen may be considered a low solubility compound.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: The highest strength which is applied for should be studied. **Background:** Pharmacokinetics is linear between 200 mg and 800 mg.
	Number of studies: In general one single dose study.

	Other design aspects: Additional studies may be necessary depending on the formulation in accordance with the Guideline on the Investigation of Bioequivalence (for example orodispersible tablets).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, C_{max} and T_{max}.
	90% confidence interval: 80.00 – 125.00% for AUC_{0-t} and C_{max}. Comparable median and range for T_{max}.

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary (BCS Class I and III), the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. *in vitro* dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).

EZETIMIBE TABLET 10 MG PRODUCT-SPECIFIC BIOEQUIVALENCE GUIDANCE

B. Requirements for bioequivalence demonstration (PKWP)*

BCS Classification	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Ezetimibe is a low solubility compound.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 10 mg **Background:** This is the only available strength.

	Number of studies: One
Analyte	☐ **parent** ☐ **metabolite** ☒ **parent + metabolite** **Background:** Ezetimibe undergoes extensive pre-systemic metabolism into ezetimibe-glucuronide. Because of extensive hepatic recirculation, the exposure of ezetimibe is less representative to evaluate the rate of absorption than the metabolite. In this particular case, total (parent + glucuronide metabolite) should be used as analyte for bioequivalence evaluation.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, C_{max}
	90% confidence interval: 80.00– 125.00%

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

US FDA PSG

- Since 2007, Product-Specific Guidances (PSGs) provide recommendations on **individual drug products** to the pharmaceutical industry for developing generic drug products.
- PSGs describe FDA's **current thinking on the evidence needed to demonstrate** that a generic drug is **therapeutically equivalent to the reference listed drug (RLD) product.**
- As of June 2021, nearly 1,900 PSGs have been published. FDA provides information on the PSG program to the general public which can be found at:
- https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

USFDA PSG

- PSGs assist the generic **pharmaceutical industry with identifying the most appropriate methodology and approaches** for their generic drug development programs, including in vivo and/or in vitro bioequivalence (BE) studies, various waiver options (such as Biopharmaceutics Classification System (BCS)-based waiver), and dissolution testing methods.
- The **clarity and transparency** provided by PSGs help **streamline generic drug product development, promote timely approval** of ANDA submissions and **increased drug competition, improving patient access to high quality and affordable medicines**

USFDA PSG

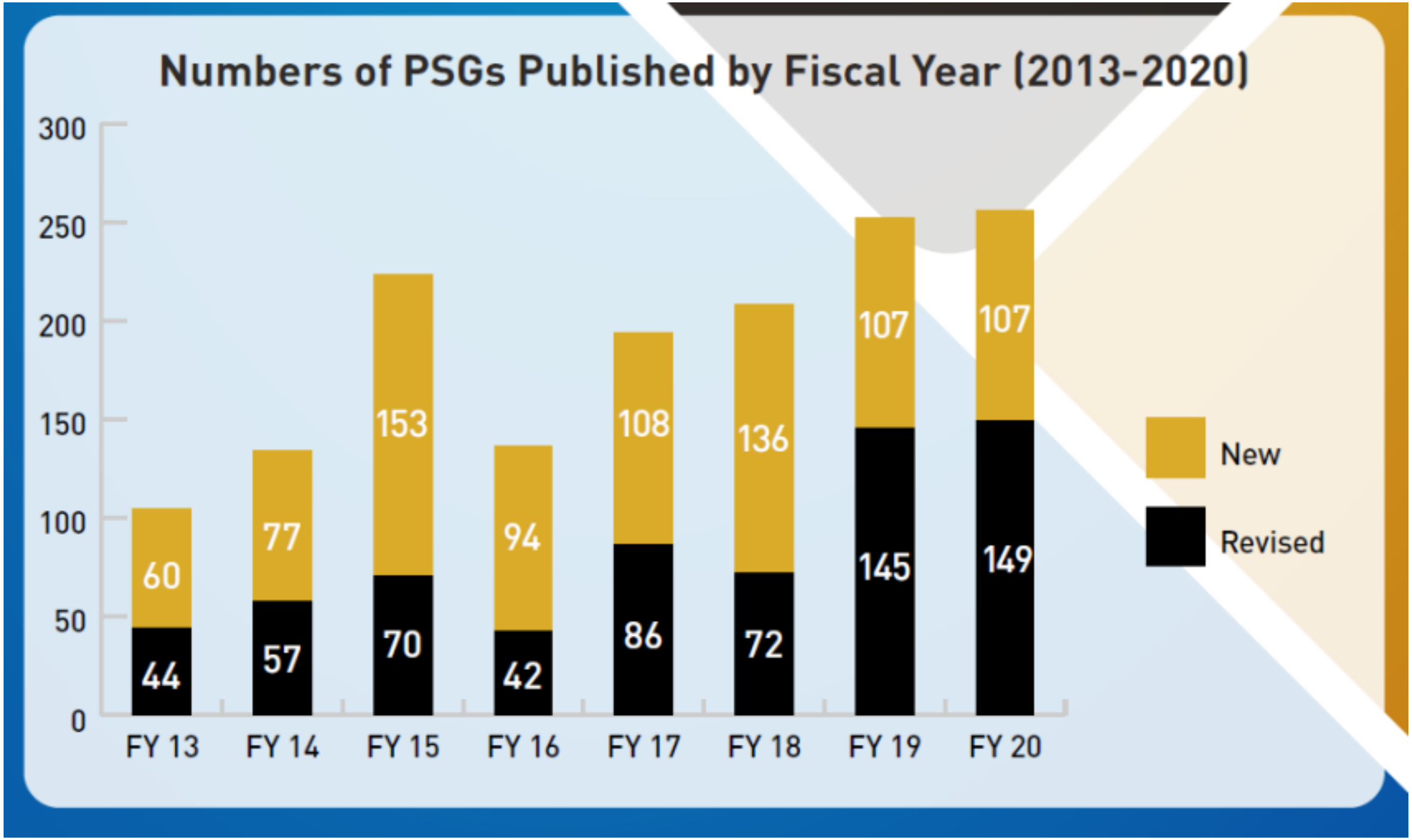
- As a commitment under the Generic Drug User Fee Amendments (GDUFA) of 2017, FDA issues PSGs for **90% of non-complex New Chemical Entities (NCEs)** that are approved on/after October 1, 2017, at least 2 years prior to the earliest allowable ANDA submission date.
- FDA issues PSGs for complex products as soon as scientific recommendations are available.
- Planned New PSGs for Complex Generic Drug Products
  - 69 products
- Planned Revised PSGs for Complex Generic Drug Products
  - 98 products

COMPLEX?

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables, implantable drugs
- Complex drug-device combination products
  - Transdermals, metered dose inhalers (MDIs)
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

USFDA PSG

- FDA issues new and revised PSGs in batches on a quarterly basis and as needed as stand-alone postings.
- Published PSGs are announced in the Federal Register and made available to the public via FDA's website found at
  - https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- FDA also provides information on upcoming new and revised PSGs for complex generic drug products on a quarterly basis at the following website.
  - https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specificguidancescomplex-generic-drug-product-development


Numbers of PSGs Published by Fiscal Year (2013-2020)
300
250
200
150
100
50
0
60
44
77
57
153
70
94
42
108
86
136
72
107
145
107
149
FY 13
FY 14
FY 15
FY 16
FY 17
FY 18
FY 19
FY 20
New
Revised

CDER Product-Specific Guidances Withdrawn Listing

Updated May 20, 2022

ACTIVE INGREDIENT	TYPE OF GUIDANCE	ROUTE AND DOSAGE FORM	RLD	DATE PSG POSTED OR REVISED	FEDERAL REGISTER NOTICE DATE
BUTENAFINE HYDROCHLORIDE	Draft	Topical Cream	21408	3/1/2012	2/1/2015
LEVONORGESTREL	Draft	IUD	203159	4/1/2014	10/1/2014
LORCASERIN HYDROCHLORIDE	Draft	Oral Tablet	022529	3/1/2015	3/4/2021
LORCASERIN HYDROCHLORIDE	Draft	Oral Tablet, ER	208524	5/1/2017	3/4/2021
LOVASTATIN; NIACIN	Draft	Oral Tablet, ER	021249	7/1/2009	4/18/2016
NIACIN; SIMVASTATIN	Draft	Oral Tablet, ER	022078	10/1/2011	4/18/2016

INITIATING EVENTS

- Recently approved New Drug
- Applications (NDAs) and supplemental NDAs
- FDA analysis of products without PSGs
- Pre-ANDA meetings
- Public requests – 100 to 150 requests year
- Comments submitted to PSG docket
- Controlled correspondences
- Citizen petitions

PRIORITIZATION

- GDUFA commitments
- Complex drug products
- Pending ANDAs without PSGs
- Drug availability and accessibility
- Public requests from generic drug industry and other stakeholders
- Public health priorities

DATA TO SUPPORT PSG DEVELOPMENT

- Pharmacokinetic (PK) and pharmacodynamic (PD) modeling
- Previous BE studies
- NDA review and labeling
- Pharmacovigilance
- GDUFA-funded research outcomes

DATA TO SUPPORT PSG DEVELOPMENT

- PSG development is a collaborative effort from multiple disciplines and offices within the FDA.
- The FDA aims to ensure that policies and regulations – and scientific standards – keep pace with the science.
- While the Office of Generic Drugs takes a leading role in PSG development, additional offices support the development and publication processes.
  - Office of Regulatory Policy
  - Office of Pharmaceutical Quality
  - Office of New Drugs
  - Office of Translational Sciences

IBUPROFEN

- https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm?event=Home.Search#letterSearchBar

REFERENCES

- CDER Guidances Webpage:
  - https://www.fda.gov/drugs/guidance-compliance-regulatoryinformation/guidances-drugs
- Guidance for Industry on Bioequivalence Recommendations for Specific Products (June 2010)
- Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions (Oct. 2020)
- PSGs for Generic Drug Development:
  - https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- Upcoming PSGs for Complex Generic Drug Product Development
  - https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidancescomplex-generic-drug-product-development