Regulatory Control of Active Pharmaceutical Ingredient (API) in Malaysia

National Regulatory Conference 2015
One World Hotel, Petaling Jaya
5 August 2015

OUTLINE

I. INTRODUCTION
II. IMPLEMENTATION
III. REQUIREMENTS
IV. API INFORMATION
V. STABILITY
VI. GUIDELINES
VII. COMMON QUESTIONS: NDP EVALUATION

I. INTRODUCTION

DEFINITION OF ACTIVE PHARMACEUTICAL INGREDIENT (API)

- Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body *(World Health Organisation (WHO))*.

II. IMPLEMENTATION

SCOPE

- All pharmaceutical products
  - New Drug Products
  - Generic Products

- **EXCLUDING**
  - Traditional products
  - Veterinary products
  - Health supplement products
  - Biological /biotechnology active substances and immunological active substances
  - Product for export only (FEO)

IMPLEMENTATION

- The National Pharmaceutical Control Bureau (NPCB) Has introduced regulatory control of APIs as part of the requirements in the product registration application.

IMPLEMENTATION DATE

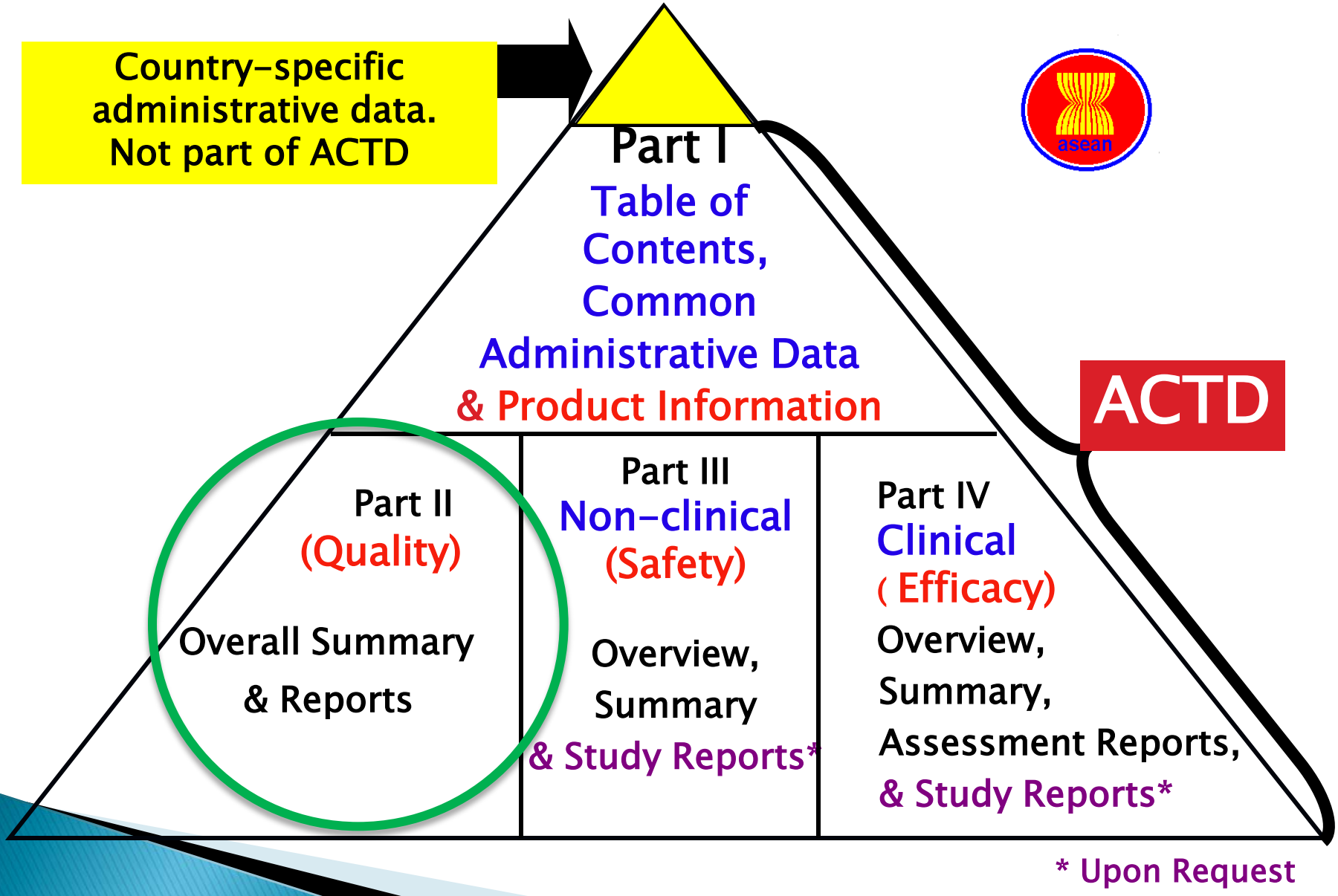
New Drug Products	• All Dosage Form : January 2012
Products Containing Scheduled Poison	• New Application (Generics) • Parenteral Dosage Form : 1 July 2014 • Oral Dosage Form : 1 July 2016 • Others : 1 July 2018 • Registered Product – All dosage Form Expire on 1 January 2020 onwards • * API Information must be submitted at least **one year before the expiry date.**
Product NOT containing Scheduled Poison	• to be determined

III. REQUIREMENTS

WHEN TO SUBMIT

- API Information requested as part of the requirements in the product registration application.

Organisation of PRODUCTS Application Dossier (ACTD)



PART 2 (Quality)

- PART 2.S (DRUG SUBSTANCE)
- PART 2.P (DRUG PRODUCT)

HOW TO SUBMIT

OPTION 1	• Full details of “Part II S ACTD”
OPTION 2	• Certificate of suitability of the European Pharmacopoeia (CEP);
OPTION 3	• Drug Master File (DMF)

WHAT TO SUBMIT

Option / Documents required	Full ACTD Part II S	DMF	CEP
ACTD	Full details of Part II S	Part II S (Open Part only)	Part II S (as deemed appropriate)
DMF From the API manufacturer/s	✗	✓ Open and Closed Part	✗
GMP Certificate/ Evidence of GMP Compliance	✓	✓	✗
CEP	✗	✗	✓
CO Analysis of API from API manufacturer/s (2 batches)	✓	✓	✓
CO Analysis of API from product manufacturer (2 batches)	✓	✓	✓

- Where any information required as per ACTD is not available, the DMF will be required.

- The DMF submitted to the NPCB should contain the information as required under sections listed in Part 2.S ACTD.

- Where a Certificate of Suitability (CEP) of Monographs of the EDQM for an API is available Drug Master File (DMF) of such API may not be required by NPCB. However, the NPCB may request any additional information about the API if it is seemed appropriate.

Processing Fee

No processing fee is required as the API application is already incorporated in the application for product registration.

IV. API INFORMATION

API INFORMATION

- Regardless of the option chosen the same information is required
- The API information submitted is compiled in the ACTD/ CTD Format
- This is regardless of whether the API is pharmacopoiel or not

API INFORMATION: ACTD FORMAT

S1 General Information
- 1.1 Nomenclature
- 1.2Structure
- 1.3 General Properties

S2 Manufacture
- 2.1 Manufacture(s)/ Site of Manufacture
- 2.2 Description of Manufacturing Process and Process Controls
- 2.3 Control of Materials
- 2.4 Controls of Critical Steps and intermediates
- 2.5 Process Validation and/or Evaluation
- 2.6 Manufacturing Process Development

S3 Characterisation
- 3.1 Elucidation of Structure and other Characteristics
- 3.2 Impurities

S4 Control of API/Drug Substance
- 4.1 Specification
- 4.2 Analytical Procedures
- 4.3 Validation of Analytical Procedures
- 4.4 Batch Analysis
- 4.5 Justification of Specification

S5 Reference Standards or Materials

S6 Container Closure System

S7 Stability

Separate API information must be provided for each API for:

- Finished product contains more than one API
- API from different manufacturing site
- API from different synthesis route

FULL DETAILS OF PART II S ACTD

- Information on the *Active pharmaceutical ingredient* sections (ACTD Part II S) , including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the product dossier.

Details on the information to be included

Please refer to:

- ASEAN Common Technical Requirements (ACTR),
- WHO Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part , and
- The ICH M4Q Technical Guidelines and other ICH Relevant Guidelines

DRUG MASTER FILE (DMF)

- DMF is a document that may be used to provide confidential detailed information of Drug Substance (API) directly to the Regulatory Authority (NPCB)
- The DMF are reviewed only in connection with application for product registration
- Information required are as sections listed under Part 2.S ACTD.
- DMF is generally created to allow an authorized party other than the holder of the DMF to refer the DMF without disclosing the contents of the file to any other party.

Letter of Access (LOA)

- The Letter of Access authorises the NPCB to refer to the DMF, in support of the application for a drug product.
- Should contain:
- The name of the drug product (product name, dosage form and product strength) to be registered;
- The local MAH responsible for finished product registration; and,
- A declaration that both the local MAH and the NPCB shall be notified of any change in the API specification or in the manufacturing process that will likely affect the product's quality or safety.

- Additional Data Request which involve the closed part will be communicated directly to the API Manufacturer

- API Manufacturer is responsible to maintain and update the DMF. The MAH should file a variation once they are notified with the changes to the DMF.

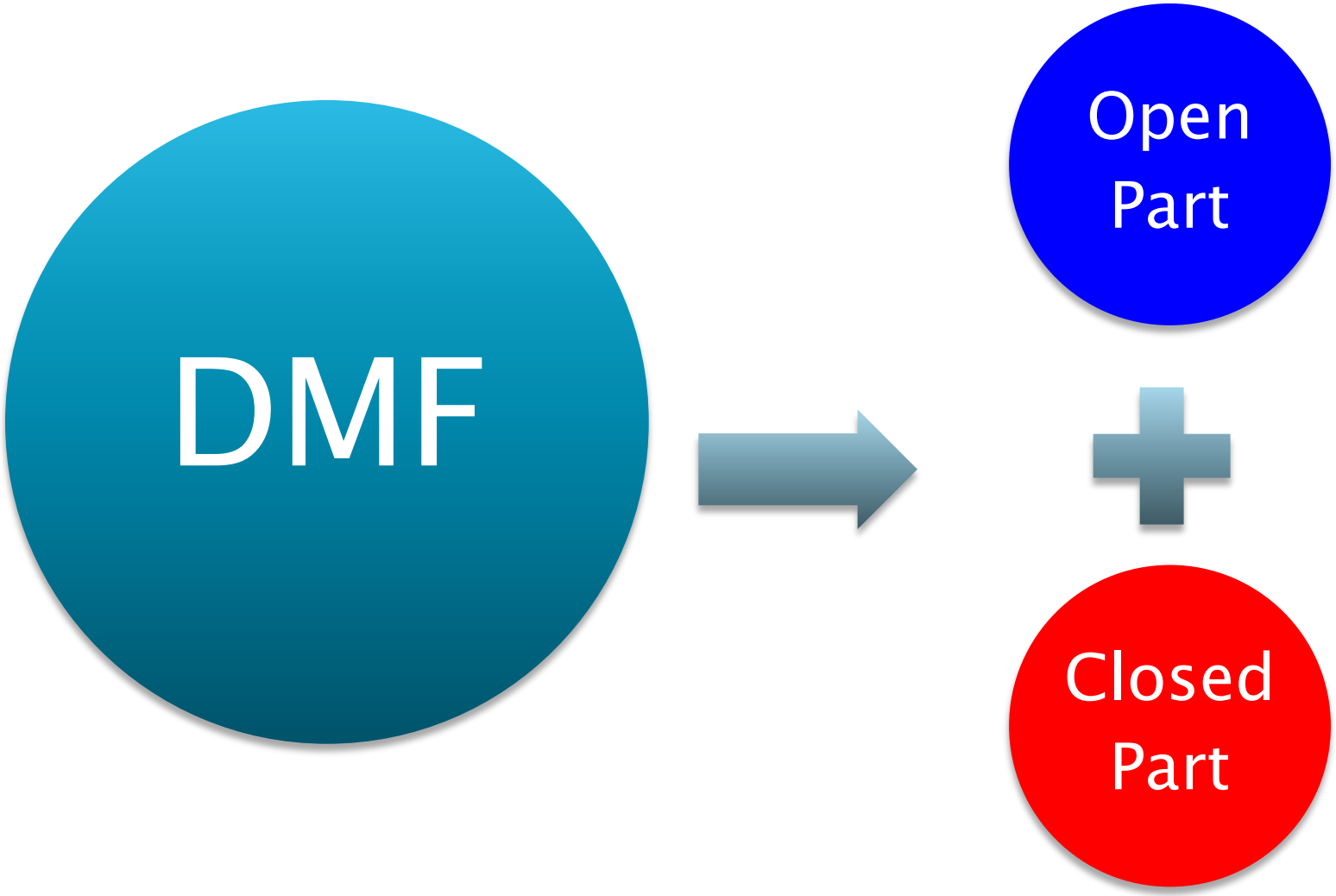

DMF
Open Part
Closed Part

TABLE1: THE DOCUMENTS REQUIRED FOR AN APPLICATION MAKING REFERENCE TO DMF

NO.	INFORMATION	From MAH	From API Manufacturer
S1	GENERAL INFORMATION…..	✓	✓
S2	MANUFACTURE 2.1 Manufacture(s)/Site of Manufacture	✓	✓
	2.2 Description of Manufacturing Process and Process Controls		✓
	2.3 Control of Materials		✓
	2.4 Controls of Critical Steps and intermediates		✓
	2.5 Process Validation and/or Evaluation		✓
	2.6 Manufacturing Process Development		✓
S3	CHARACTERISATION ……	✓	✓
S4	CONTROL OF API/DRUG SUBSTANCE …	✓	✓
S5	REFERENCE STANDARDS OR MATERIALS	✓	✓
S6	CONTAINER CLOSURE SYSTEM	✓	✓
S7	STABILITY…	✓	✓

Closed Part

From the MAH:

- Open part of the DMF *from the MAH*, as part of the submitted product dossier

From the API Manufacturer:

- Complete DMF (open and closed part)

CERTIFICATES OF SUITABILITY (CEP)

- CEP stands for certification of suitability of European Pharmacopoeia monographs/Certificate of Pharmacopoeia.
- The CEP is a document that is used to demonstrate that the purity of a given substance produced by a given manufacturer is suitably controlled by the relevant monograph(s) of the European Pharmacopoeia.
- By demonstrating grant a CEP for given API, the suppliers of the API can prove such suitability to their pharmaceutical industry clients and the NPCB.

The PRH should include a copy of the most current CEP in the dossier, together with the following:

- A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and ;
- A declaration from the API manufacturer that the local MAH and the NPCB shall be notified should there be any future change in the API specifications in the manufacturing process that is likely to affect the product's quality or safety.

Note: All such written statements must state the name of the drug product (product name, dosage form and product strength) to be registered and the local MAH responsible for finished product registration.

V. STABILITY

STABILITY DATA OF API

- At least 3 primary batches.
- Data should include:
  - Batch details (e.g., batch number, date of manufacture);
  - The general test methodology (e.g., duration of study, storage conditions of temperature and humidity, time points when samples were removed for analysis etc.);
  - The analytical test methods (e.g., assay method of quantitation, determination of degradation products, moisture etc);
  - Validation of test methods;
  - Results of tests; and,
  - Conclusions.

- In circumstances where an API retest period has not been established and complete real time stability data is not available at the time of submission, the minimum stability data required are as follows:

- At least 12 months of real time data and 6 months of accelerated data on at least **three** primary batches of the API ;
- The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.

**In view of this, the re-test date may be extended beyond the end of real time studies which can be extrapolated not more than 12 months covered by the real time data.*

VI. GUIDELINES

GUIDELINES

- MALAYSIA DRUG REGISTRATION GUIDANCE DOCUMENT (Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients (API))
- ASEAN Common Technical Requirements (ACTR)
- WHO GUIDELINES
- ICH QUALITY GUIDELINES
- EDQM GUIDELINES
- OTHERS

IMPORTANT GUIDELINES/ REFERENCE

- ASEAN Guidance on ACTD
- WHO Guideline On Submission Of Documentation For A Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part
- WHO Technical Report Series, No. 953, 2009 Annex 2 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products
- ICH QUALITY GUIDELINE
  - Stability Q1A–Q1F
  - Analytical validation Q2
  - Impurities in New Drug Substance Q3A
  - Impurites: Guideline for Residual Solvent Q3C
  - Impurities: Guideline for Metal Impurites
  - Specifications Q6A
- Pharmacopoeias (International Pharmacopoeia , BP, USP, EP/Ph Eur, JP, NF)

VII. COMMON QUESTIONS

NEW DRUG PRODUCTS
2012-2013

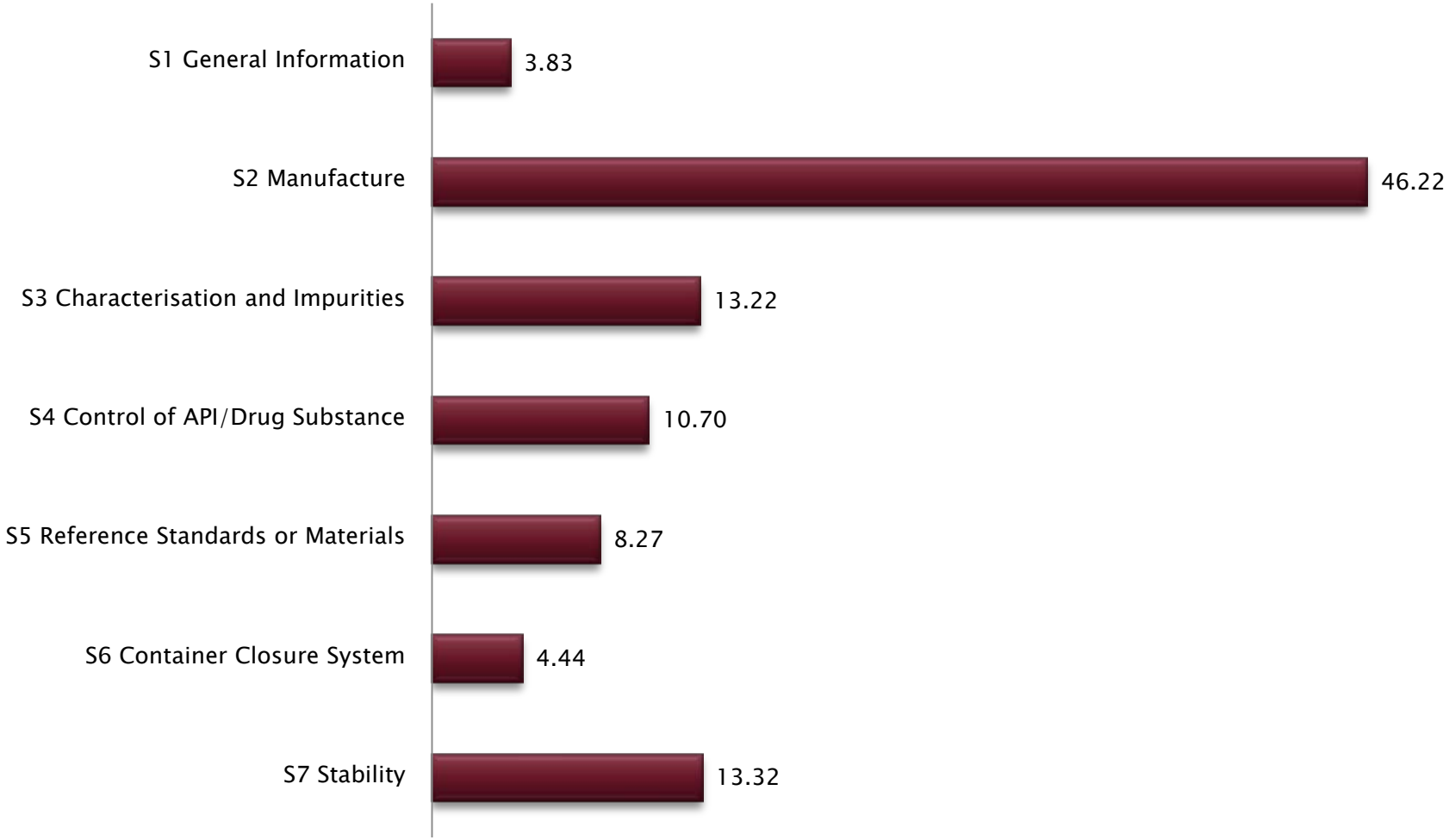
NEW DRUG PRODUCTS 2012-2013

- Total No. of Products: 52
- No. of "List of Additional Data Request": 69

(* List per API Manufacturer)

- No. of Questions: 991

Percentage of Questions by ACTD Section



TOP 3

- Manufacture (S2)
- Stability (S7)
- Characterization and Impurities (S3)

Manufacturing Process (S2)

- A detailed manufacturing scheme that indicates molecular formulae, molecular weights, chemical structures of starting materials, intermediates and the API including stereochemistry, reagents, catalysts and solvents used in each step.

- A detailed narrative of each steps

Manufacturing Process (S2)

- Quantity of each material
- The maximum batch size
- Re-processing and re-working
- Recovery of materials or solvents
- Starting material information
- Blending of batches

Stability (S7)

- Shelf-life and Storage Condition was not proposed
- Stress testing Study

Characterization and Impurities (S3)

- The information for API Polymorphism
- A detailed discussion on potential impurities
- Contamination of Benzene in certain Solvent
- Discussion on potential genotoxic impurities
- Discussion for Impurities which exceed Qualification threshold

Thank You