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Purpose of the document:

This document aims to highlight those areas where the South African (ZA) CTD medicine registration application goes beyond the information which is routinely supplied in the EU CTD dossier. It is not intended to be a comprehensive overview of all the information required to be included the ZA registration application, but rather to alert a European regulatory partner about those instances where further ZA-specific information needs to be taken into consideration, and to assist them to locate further details regarding these requirements in the various ZA registration guidelines.

All the South African registration guidelines can be found on the MCC website at: www.mccza.com. It is advisable to always refer to this website in case new versions of the guidelines mentioned herein have been released.

Introduction:

The South African Health Authority (MCC) has a number of unique and additional requirements which are imposed upon applicants and therefore it is usually necessary to supplement the core regulatory data package provided by partners in Europe and elsewhere. ***Particular attention should be paid to the "regional information" sections in the attached table.***

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
MODULE 1	**ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION**	NA
-	***This Module is prepared locally; however support is required to obtain the following information:***	2.24 Guidance Module 1 Jun10 v2
1.2.2.3 Overview of batches used for product development	Remark: it is not always possible to extract all of the information required for the below table from the Development Pharmaceutics report, Batch Analysis report and Stability reports which are included in the EU CTD. **Dossier product batch information** The following are particulars which clarify the pharmaceutical development of the dosage form, from which data furnished in the under-mentioned Modules were derived: Table follows overleaf/…..	2.24 Guidance Module 1 Jun10 v2 (pg 17)

<table>
<tr><td>Module No.</td><td rowspan="2">Title</td><td>Standard EU information sufficient
Y/N</td></tr>
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<tr><td>7.**Site 1 of API 1</td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr><td>10.Site 2 of API 2</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
* Experimental, pilot or production
** Add as many rows as necessary for APIs and API manufacturing sites
</td><td></td></tr>
<tr><td>1.2.2.6</td><td>Copy of written confirmation from the manufacturer of the API to inform the applicant in case of modification of the manufacturing process or specifications</td><td>-</td></tr>
</table>

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
No unauthorized change to API process	This declaration needs to confirm that a formal agreement exists between the applicant of the medicine and each manufacturer of the active pharmaceutical ingredient (API) which ensures that information will be communicated between them and to the MCC before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except when permitted by the MCC's post-registration guidelines relating to changes to medicines, such changes will not be made to the API(s) to be used in manufacture of medicines destined to be distributed in South Africa before written approval is granted by the MCC. Both parties understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines containing this material in South Africa. *[This could for example be covered in the technical agreement with the API supplier].*	2.24 Guidance Module 1 Jun10 v2 (pg 18)
1.2.2.7	**Copy of EMEA certificate for a Vaccine Antigen Master File (VAMF)**	-
VAMF	Copy to be provided	2.24 Guidance Module 1 Jun10 v2 (pg 18)
1.2.2.8	**Copy of EMEA certificate for a Plasma Master File (PMF)**	-
Plasma Master File	Copy to be provided	2.24 Guidance Module 1 Jun10 v2 (pg 18)
1.4	**Information about the experts**	2.24 Guidance Module 1 Jun10 v2 (pg 20)
1.4.1	Declaration signed by the expert - Quality	Y
Info -expert	Information about the Expert - Quality	Y
1.4.2	Declaration signed by the expert - Non-clinical	Y
Info -expert	Information about the Expert - Non-clinical	Y
1.4.3	Declaration signed by the expert - Clinical	Y

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
Info -expert	Information about the Expert - Clinical	Y
1.7	**Good manufacturing practice**	-
1.7.1 Inspection dates	We need a list of the dates of inspection by the Health Authorities of either FDA, MHRA, TGA, EU, Canada, PIC/s country, at each site.	2.24 Guidance Module 1 Jun10 v2 (pg 23)
1.7.2 Inspection reports	According to the guideline we are required to provide copies of inspection reports, not older than 3 years, from the Health Authorities of either FDA, MHRA, TGA, EU, Canada, PIC/s country, at each site.	2.24 Guidance Module 1 Jun10 v2 (pg 23)
1.7.3 GMP certificate	Include the latest GMP certificate, not older than 3 years, for manufacturer/s and packer/s or a copy of the appropriate manufacturing licence.	2.24 Guidance Module 1 Jun10 v2 (pg 23)
Site Master File	A copy of the site master file (SMF) for the manufacturing, packaging and quality control sites is required to be submitted to the SA health authority separately from the application for registration of the medicine. The heath authority issues site master file reference numbers which then have to be provided in the "Module 1: Administrative Information; Application Form" which is included with the registration application for the medicine. The health authority generally accepts site master files in the WHO or PIC format. An example of the format preferred by the MCC is provided in a separate guideline provided on the MCC website. However, the HA is quite flexible with regard to the format of the SMFs.	-
1.7.4	**Finished Product Release Control (FPRC) tests**	-
1.7.4.1 Post-importation retesting of ID and assay	For imported products at least the identification and assay of the API content should be performed by an approved laboratory (FPRC) after importation. This is to verify that the product has not been affected adversely during transportation. Exemption from this requirement may be applied for, either with the initial registration application or later after registration, if the requirements according to the "Post-Importation Testing of Medicines guideline" can be fulfilled.	2.24 Guidance Module 1 Jun10 v2 (pg 23)

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
1.7.4.2 Confirmation of compliance	For every batch of product sent to ZA, a declaration of batch manufacturing record compliance needs to accompany the certificate of analysis.	2.24 Guidance Module 1 Jun10 v2 (pg 23)
1.7.5 Technical agreements	We need a declaration confirming that contracts (i.e. technical agreements) with all third party manufacturer/s and/or packer/s are in place, and these may need to be made available at short notice for HA inspection purposes.	2.24 Guidance Module 1 Jun10 v2 (pg 23)
1.7.6 WHO-type CPP	Certificate of a Pharmaceutical Product (CPP) in terms of the WHO certification scheme (Free Sales Certificate) and / or a copy of the registration or marketing authorisation certificate for the product if applicable. *[Remark: the South African application is not dependant on the availability of a CPP, but if the product is already available in the country of manufacture, the CPP or copies of the registration certificates from recognized regulatory authorities should be submitted – refer also to point 1.10 below].*	2.24 Guidance Module 1 Jun10 v2 (pg 23)
1.7.10	**Sample and documents**	2.24 Guidance Module 1 Jun10 v2 (pg 24)
1.7.10.1 Registration sample	All medicine applications for registration must include a sample of a unit pack. One sample of the smallest pack size from each packaging system must be submitted.	-
1.7.10.2 Batch record	Batch manufacturing and packaging record of the sample must be available at the local applicant company in case of HA inspection (refer to 1.7.11).	-
1.7.10.3 CoAs	Include the CoA of the finished pharmaceutical product (FPP) and of the active pharmaceutical ingredient/s (API) used in the sample. Ensure that the batch number on the CoA corresponds with the batch number on the sample.	-
1.7.11 Product master file	We have to keep the master batch manufacturing and packaging documents in a Product Master File in case of HA inspection.	2.24 Guidance Module 1 Jun10 v2 (pg 24)

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
1.7.12 INCB permit	Include a duly certified permit to manufacture INCB-controlled substances.	2.24 Guidance Module 1 Jun10 v2 (pg 24)
1.9	**Individual patient data - statement of availability**	-
Individual patient data	We need to include a statement that raw clinical and pre-clinical data have been removed from the application and that individual patient data are available on request (i.e. within 15 working days). Appendices to non-clinical and clinical reports are not required to be submitted in ZA. The exception is for bioequivalence studies where certain individual patient data for plasma concentrations and derived data are required, and where trial report appendices do need to be submitted (e.g. analytical validation and statistical reports) – refer to the Biostudies guideline for further details.	2.24 Guidance Module 1 Jun10 v2 (pg 25)
-	Individual patient data may be requested by the MCC: • to support a particular study if, during the evaluation, there is any reason to doubt the analysis or conclusions reached; • if, after registration, the application is selected for auditing of the summary results and conclusions. If a marketing application for the medicine has been rejected in the USA, UK, Sweden, Australia, Canada, EU, or Japan, before or during the South African evaluation process, for reasons related to the clinical data in any way, full individual patient data must always be available and may be required to be submitted in South Africa. In the event that the South African evaluation process has commenced, applicants should contact the Registrar of Medicines.	2.24 Guidance Module 1 Jun10 v2 (pg 25)
1.10	**Foreign registration status**	-
1.10.1	**List of countries in which an application for the same product as being applied for has been submitted**	-
Foreign registration status	We need to include a list of countries in which an application for the same product as being applied for in South Africa has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case.	2.24 Guidance Module 1 Jun10 v2 (pg 26)
1.10.2	**Registration certificates or marketing authorisation**	-

Module No.	Title	Standard EU information sufficient Y/N
Key word		**Source of ZA requirement**
Foreign registration – recognized countries	In the case of registration in the country of origin (= country where manufactured), USA (FDA), UK (MHRA), Sweden (MPA), Australia (TGA), Canada (Health Canada), EU (EMEA), Japan (MWH) copies of the registration certificates or marketing authorisation should be supplied.	2.24 Guidance Module 1 Jun10 v2 (pg 26)
Extract from "General information" guideline for comparison	*The Council aligns itself with* - *the following regulatory authorities: USA (FDA), UK (MHRA), Sweden (MPA,) Australia (TGA), Canada (Health Canada), European Union (EMA and Mutual Recognition procedure, excluding National procedure), Switzerland (Swissmedic) and Japan (MWH).* - *members of the PIC/S (Pharmaceutical Inspection Co-operation Scheme) for quality matters relating to GMP.*	*2.01 General information Jun10 v6. (pg 14)*
1.10.3	**Foreign prescribing and patient information**	-
Foreign PI	In the case of marketing authorisations in country of origin (= country where manufactured), USA, UK, Sweden, Australia, Canada, EU, Japan, copies of relevant prescribing and patient information should be supplied, e.g. the Canadian Product Monograph, the Summary of Product Characteristics (SPC) in the EU, UK, and Sweden, Prescribing Information (PI) in USA. If the overseas SPC, monograph or PI has not been approved at the time the application is lodged in South Africa, a draft document may be provided. The approved overseas SPC, monograph or PI should then be supplied to the MCC as they become available. (English translations of foreign texts are mandatory).	2.24 Guidance Module 1 Jun10 v2 (pg 26)
1.10.4	**Data set similarities**	-
Data set	We need a summary of the similarities / differences in the data packages submitted in other countries.	2.24 Guidance Module 1 Jun10 v2 (pg 26)
1.10.5	**Statement on application rejection, withdrawal or repeated deferral**	-
Foreign registration rejections	We are required to declare whether a marketing application for the medicine has been rejected in the countries listed under 1.10.2 prior to submission of the application in South Africa. If the medicine has been rejected, repeatedly deferred or withdrawn, then the MCC must be informed and the reasons supplied	2.24 Guidance Module 1 Jun10 v2 (pg 26)
1.10.6	**Reason for non-registration in country of origin**	-

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
Country of origin	If no application has been submitted for registration in the country of origin (= country where manufactured), include a statement to provide the reason for this decision.	2.24 Guidance Module 1 Jun10 v2 (pg 26)
1.11	**Bioequivalence trial information**	-
Bioequivalence studies	We are required to provide the following details in cases where the proof of efficacy in the application is based on bioequivalence. Please also refer to the remarks provided below the table in the guideline. *[Refer also to point* **3.2.R.1** *below]*	2.24 Guidance Module 1 Jun10 v2 (pg 27)
1.11.1	Study Title(s) (or brief description giving design, duration, dose and subject population of each study)	As per 1.11 above
1.11.2	Protocol and study numbers	As per 1.11 above
1.11.3	Investigational products (test and reference) details, including	As per 1.11 above
1.11.3.1	active ingredient	As per 1.11 above
1.11.3.2	strength	As per 1.11 above
1.11.3.3	dosage form	As per 1.11 above
1.11.3.4	manufacturer	As per 1.11 above
1.11.3.5	batch no.	As per 1.11 above
1.11.3.6	expiry or retest date	As per 1.11 above
1.11.3.7	country in which procured	As per 1.11 above
1.11.3.8	confirmation that the test product formulation and manufacturing process is that being applied for	As per 1.11 above
1.11.3.9	proof of procurement of the biostudy reference product	As per 1.11 above
1.11.4	Name and address of the Research Organisation(s) / Contract Research Organisation(s) where the bioequivalence studies were conducted	As per 1.11 above
1.11.5	Sponsor and responsible sponsor representative: name and address, contact details	As per 1.11 above
1.11.6	Duration of Clinical phase: dates of dosing and last clinical procedure	As per 1.11 above

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
1.11.7	Date of final report	As per 1.11 above
1.12	**Paediatric development program**	
Paediatric information	Please state whether there is a paediatric development program for this medicine and if so, the relevant sections of the dossier.	2.24 Guidance Module 1 Jun10 v2 (pg 28)
MODULE 2	**CTD SUMMARIES**	Y
MODULE 3	**QUALITY**	-
3.1	**TABLE OF CONTENTS OF MODULE 3**	-
3.2	**BODY OF DATA**	-
3.2.S	**Active Pharmaceutical Ingredient**	-
3.2.S.1	**General Information**	-
3.2.S.1.1	**Nomenclature**	Y
3.2.S.1.2	**Structure**	Y
3.2.S.1.3	**General Properties**	N
API solubility	The physical and chemical properties of the API, including e.g. solubility, particle size, hygroscopicity should be indicated. The solubility of each API should be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The solvents should include water and the solvent(s) relevant to the product formulation. If the API has a low solubility in water in accordance with the BCS definition the solubility should be quantified (mg/ml). Evidence of occurrence of isomers, chirality and polymorphism, where applicable, should be provided. The absence of isomers, chirality and/or polymorphism should be confirmed	2.25 PA CTD Jun 10 v1 (pg 6)
3.2.S.2	**Manufacture**	-
3.2.S.2.1	**Manufacturer(s)**	Y

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
API manufacturer	The name, business and physical address of each manufacturer of the API being applied for (including any intermediate manufacturer) should be stated. No API from any source, other than the approved source(s), may be used.	2.25 PA CTD Jun 10 v1 (pg 7)
3.2.S.2.2	**Description of Manufacturing Process and Process Controls**	Y
3.2.S.2.3	**Control of Materials**	Usually not submitted
-	**Specifications and Analytical Procedures for Starting Materials**	Usually not submitted
-	Only required to be submitted for biological medicines.	Y
3.2.S.2.4	**Controls of Critical Steps and Intermediates**	Y
-	**Specifications and Analytical Procedures for Drug Substance Intermediates**	Y
3.2.S.2.5	**Process Validation and/or Evaluation**	Y
3.2.S.2.6	**Manufacturing Process Development**	Y
3.2.S.3	**Characterisation**	Y
3.2.S.3.1	**Elucidation of Structure and other Characteristics**	Y
	Elucidation of Structure.	Y
Well known API – structure	Proof of correctness of structure for a well-known API, e.g. IR spectrometric comparison against an official standard may be acceptable	2.25 PA CTD Jun 10 v1 (pg 7)
-	Physicochemical Characteristics	Y
-	Solid State Forms	Y
3.2.S.3.2	**Impurities**	Y
3.2.S.4	**Control of active pharmaceutical ingredient**	
3.2.S.4.1	**Specification**	N
API particle size & solubility	Specifications and the control procedures for the particle size of APIs which have a low solubility in water in accordance with the BCS definition should be submitted and the solubility quantified unless justified. Particle size should be stated in SI units (μm). Exemption from this requirement may be granted if the API is administered as a clear solution	2.25 PA CTD Jun 10 v1 (pg14)

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
API specs in table	The HA requires the specifications in tabulated format – not narrative.	2.25 PA CTD Jun 10 v1 (pg 7)
3.2.S.4.2	**Analytical Procedures**	Y
3.2.S.4.3	**Validation of Analytical Procedures**	Y
3.2.S.4.4	**Batch Analyses**	N
API CoAs	Submit valid certificates of Analysis (CoAs) from the API manufacturer relating to at least two batches. CoAs for at least two of these batches should be within the retest period at the time of submission of the application.	2.25 PA CTD Jun 10 v1 (pg 8)
3.2.S.4.5	**Justification of Specification**	Y
3.2.S.5	**Reference Standards or Materials**	2.25 PA CTD Jun 10 v1 (pg 8)
Requirements reference standards	For NCEs and well-known non-compendial APIs at least the following information on the primary reference standard should be presented: Purification method if applicable Establishment of purity (recrystallisation) CoA, with a potency statement	Y
3.2.S.6	**Container Closure System**	-
-	Description of the Container Closure System	Y
-	Container Closure System Suitability	Usually not submitted
-	**Specifications and Analytical Procedures for Container/Closure System**	Usually not submitted
3.2.S.7	**Stability**	-
3.2.S.7.1	**Stability Summary and Conclusions**	Y
Storage requirements for API	The storage requirements for the API as specified by the manufacturer of the API and/or prescribed in the pharmacopoeia or acceptable standard reference should be stated and a description of the API container closure system be included. If a specific storage temperature is not specified in any acceptable reference, an instruction to protect from excessive heat, freezing and moisture and light should be included unless justified. The proposed retest period should be stated	2.25 PA CTD Jun 10 v1 (pg 8)
3.2.S.7.2	**Post-approval Stability Protocol and Stability Commitment**	Y
3.2.S.7.3	**Stability Data**	Y

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
-	Stress Stability Data	Y
-	Accelerated and Long-Term Stability Data	Y
3.2.P	**DRUG PRODUCT**	-
3.2.P.1	**Description and Composition of the Drug Product**	N
IPIs not present in final dosage form	Inactive pharmaceutical ingredients (IPIs) not present in the final product should be indicated, i.e. we need information on the quantity of purified water (per tablet) or other granulating liquid used in the manufacturing process. Although the water is evaporated during the manufacturing process and therefore not present in the final product, we are required to declare the theoretical quantity of water utilised per tablet in the formulation	2.25 PA CTD Jun 10 v1 (pg 9)
Grade of IPI	The grade of IPIs, also when a pharmacopoeial monograph covers more than one grade, (e.g. viscosity of methyl cellulose) and the type of water (e.g. purified, WFI), where relevant, should be indicated.	2.25 PA CTD Jun 10 v1 (pg 9)
Composition of mixtures	We need to supply details of the quantitative composition of commercially purchased blends like Opadry products and colourants used in the manufacturing of the products (in some cases only the qualitative composition is provided in the EU CTD), as it is a requirement of our Health Authority to include this information, for example as an appendix to the formulation of the product	2.25 PA CTD Jun 10 v1 (pg 9)
Potency calculations	If a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the active will depend on the potency and the IPI(s) that will be used to adjust the bulk quantity should be made. The manner in which the adjustment will be made should also be specified. Potency calculations and formulae, where applicable, should be included and should also be shown in Module 3.2.P.3 (Manufacturing Procedure). If the moisture content or other characteristic of an IPI is relevant to the quantity of the IPI used in the formulation, this should be mentioned in a footnote. Overages in the formulation need to be explained.	2.25 PA CTD Jun 10 v1 (pg 10)
CI numbers for colourants	The Colour Index Numbers of colourants should be included in the formulation.	2.25 PA CTD Jun 10 v1 (pg 10)
3.2.P.2	**Pharmaceutical Development**	Y
-	Pharmaceutical Development	Y

Module No. Key word	Title	Standard EU information sufficient Y/N Source of ZA requirement
-	Clinical Trial Formulations and Batches	Y
3.2.P.3	**Manufacture**	-
3.2.P.3.1	**Manufacturer(s)**	Y
Third party sites	We need confirmation that all manufacturing, packaging and QC processes take place at the stated sites, and that there are no third parties involved.	-
3.2.P.3.2	**Batch Formula**	Y
Batch size in dosage units	The HA requires that the batch size is also expressed in number of dosage units.	2.25 PA CTD Jun 10 v1 (pg 12)
Potency calculations	Potency calculations and formulae, where applicable, should be included.	2.25 PA CTD Jun 10 v1 (pg 10)
3.2.P.3.3	**Description of Manufacturing Process and Process Controls**	-
-	Description of the Manufacturing Process	N
Detailed manufacturing procedure	The description of the manufacturing process to include the type and size of manufacturing equipment (including sieve sizes in metric units), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. rotation speed or rpm) and other relevant detail should be indicated. The frequency of all in-process control tests (analytical, microbiological, physical, packaging and labelling) should be specified and any potency calculations included.	2.25 PA CTD Jun 10 v1 (pg 12)
Master documents	<u>In addition</u>: We require either a copy of the Master Batch Manufacturing and Packaging Documents or executed manufacturing and packaging records for a specific batch should be available for inspection. In the latter case the records pertaining to the registration sample are required. These are not submitted to the HA, but are retained in an in-house product master file.	2.25 PA CTD Jun 10 v1 (pg 12 & 28)
	Packaging Procedure	Y

Module No. / Key word	Title	Standard EU information sufficient Y/N / Source of ZA requirement
Additional manufacturing or packaging sites	If more than one site is involved in any of the manufacturing or packaging processes, the complete name and physical address of each site should be given and the various stages of manufacturing and packaging at each site clearly identified and a formal declaration of the similarity of the manufacturing and/or packaging processes used at the different sites would be needed to include in Module 3.2.R.4. If the processes at the different sites are not identical (i.e. it is not possible to provide the formal declaration), then additional comparative dissolution studies would be needed to demonstrate the similarity of the FPP manufactured at the various sites. These data would be submitted in the ZA CTD regional module, section 3.2.R.1.3.2.	2.25 PA CTD Jun 10 v1 (pg 12 & 26)
3.2.P.3.4	**Controls of Critical Steps and Intermediates**	Y
-	**Specifications and Analytical Procedures for Drug Product Intermediates**	-
-	Specifications for intermediates	Y
-	Analytical procedures for intermediates	Y
-	Validation of Analytical Procedure for Intermediates	Y
-	**Justification for Drug Product Intermediate Specifications**	Usually not submitted
3.2.P.3.5	**Process Validation and/or Evaluation**	-
Validation	A process validation protocol (VP) or report (VR) should be submitted. If the VP is submitted the VR should be submitted only if and when requested by the Regulatory Authority. If different sterilisation methods are used, validation data of each method should be provided. Microbial challenge is generally included in the validation programme of autoclaving cycles.	2.25 PA CTD Jun 10 v1 (pg 13)
3.2.P.4	**Control of Inactive Pharmaceutical Ingredients (IPI)**	N
3.2.P.4.1	**Specifications**	N
Colourants and flavourants	For colourants and flavourants we require at least a specification and control procedure regarding chemical identification and a statement that it complies with the directives of the EU or the register of the FDA.	2.25 PA CTD Jun 10 v1 (pg 14)

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
Propylene glycol and glycerine TS	The absence of diethylene glycol should be specified for propylene glycol and glycerine if the dosage form is for oral or parenteral administration.	2.25 PA CTD Jun 10 v1 (pg 14)
Grade of IPI	We need information concerning the "grade" of certain raw materials like microcrystalline cellulose (e.g. PH101 or PH102). It is a requirement of our Health Authority to declare this in the formulation. We also need to know how the "grade" of certain ingredients like microcrystalline cellulose is controlled e.g. are additional tests performed on the microcrystalline cellulose (apart from those stated in the Ph. Eur, for example) to ensure receipt/ use of the correct grade.	2.25 PA CTD Jun 10 v1 (pg 14)
Minimum testing requirements in ZA for API and IPI	We need a declaration that the following minimum requirements will be met by the laboratory responsible for releasing the APIs and IPIs: a) Identification and assay of the APIs will be performed irrespective of the possession of a CoA from the manufacturer. b) Identification of the IPIs will be performed irrespective of the possession of a CoA from the supplier. c) Any tests included in the specifications and not included in a valid CoA will be performed. For IPIs for which a conclusive identification test is not described, all parameters that are specific to the identification of such ingredients should be listed and the tests performed irrespective of the possession of a CoA from the supplier.	2.25 PA CTD Jun 10 v1 (pg 14-15)
Frequency of water testing	Frequency of testing water is required. The following minimum testing requirements are applicable: Water should be tested at least once a week for microbiological contaminants and daily, or just before use, for conductivity, and total organic carbon if applicable	2.25 PA CTD Jun 10 v1 (pg 15)
Talc TS	Talc should be declared and specified asbestos-free. *[Test to be included in the relevant IPI specification to ensure batch to batch conformance. The HA requirement is in line with the EP which states the following: "Talc derived from deposits that are known to contain associated asbestos is not suitable for pharmaceutical use. The manufacturer is responsible for demonstrating by the test for amphiboles and serpentines that the product is free from asbestos". See EP monograph for further details].*	2.25 PA CTD Jun 10 v1 (pg 28)
3.2.P.4.2	**Analytical Procedures**	Y

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
-	**Certificates of Analysis for IPIs**	Usually not submitted
3.2.P.4.3	**Validation of Analytical Procedures**	Y
3.2.P.4.4	**Justification of Specifications**	Y
3.2.P.4.5	**Excipients of Human or Animal Origin**	Y
3.2.P.4.6	**Novel Excipients**	Y
3.2.P.5	**Control of Drug Product**	-
3.2.P.5.1	**Specification(s)**	N
Scored tablets	Specification to be provided for the divisibility of the scored tablet with the relevant mass uniformity of the divided tablet.	2.25 PA CTD Jun 10 v1 (pg 15)
Intactness of coating	Specification to be provided for intactness of coating in the case of coated tablets if the coating has a protective purpose; if not appropriate for a particular product (e.g. film coat) a motivation should be included.	2.25 PA CTD Jun 10 v1 (pg 15)
Assay (mg and %)	The limits of acceptance for the content of each active ingredient should be expressed as a percentage of the label claim and as a quantity per dosage unit / suitable unit of mass or volume. Limits equal to or more than 10 % of the label claim should be justified if not vitamins.	2.25 PA CTD Jun 10 v1 (pg 16)
Dissolution specification	Batch release and stability specifications for all solid oral dosage forms, including chewable tablets, and suspensions where applicable, should include a requirement for the dissolution of the active pharmaceutical ingredient(s), generally single point for immediate release, multipoint for modified release.	2.25 PA CTD Jun 10 v1 (pg 16)
3.2.P.5.2	**Analytical Procedures**	Y
3.2.P.5.3	**Validation of Analytical Procedures**	Y

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
3.2.P.5.4	**Batch Analyses**	N
Actual CoA for FPP	A complete analysis report or CoA for one batch (pilot or production) of the final product should be submitted with the application. Usually the CoA pertaining to the registration sample is provided.	2.25 PA CTD Jun 10 v1 (pg 17)
Retesting of imported products	For imported products at least the identification and assay of the API content should be performed by an approved laboratory after importation. This is to verify that the product has not been affected adversely during transportation. Exemption from this requirement may be applied for according to the Post-Importation Testing of Medicines guideline.	2.25 PA CTD Jun 10 v1 (pg 18)
3.2.P.5.5	**Characterisation of Impurities**	Y
3.2.P.5.6	**Justification of Specification(s)**	Y
3.2.P.6	**Reference Standards or Materials**	Y
3.2.P.7	**Container Closure System**	Y
-	**Specifications and Analytical Procedures**	N
Supplier tests	The tests performed by the supplier of the packaging material should be indicated and a description of the control procedures performed by the manufacturer of the final product given. *[It is helpful to receive a CoA from the packaging material supplier to determine which tests they perform]*.	2.25 PA CTD Jun 10 v1 (pg 18)
Bulk container	If the product is packed in bulk containers, the type of material of the container, should be stated. Please note that if the final product is stored for 25 % or more of the approved shelf life in the bulk container, then we are required to submit stability data of the final product in the bulk containers concerned.	2.25 PA CTD Jun 10 v1 (pg 18) & 2.05 Stability Jun10 v5 (pg 9)
Child-protective measures	Child-protective measures must be employed with regard to the retail sale of salicylates, paracetamol and iron tablets or capsules. Smaller sales packs and blister packaging are regarded as suitable child protective measures	2.25 PA CTD Jun 10 v1 (pg 18)
	Certificate of Analysis	Usually not submitted

<table>
<tr><td>Module No.</td><td rowspan="2">Title</td><td>Standard EU information sufficient Y/N</td></tr>
<tr><td>Key word</td><td>Source of ZA requirement</td></tr>
<tr><td>3.2.P.8</td><td>Stability for FPP</td><td>-</td></tr>
<tr><td>3.2.P.8.1</td><td>Stability Summary and Conclusion</td><td>Y</td></tr>
<tr><td>3.2.P.8.2</td><td>Post-approval Stability Protocol and Stability Commitment</td><td>Y</td></tr>
<tr><td>3.2.P.8.3</td><td>Stability Data</td><td>Y</td></tr>
<tr><td>-</td><td>Stress Stability Data</td><td>Y</td></tr>
<tr><td>-</td><td>Accelerated and Long-Term Stability Data</td><td>Y</td></tr>
<tr><td>-</td><td>In-use Stability Data</td><td>Y</td></tr>
<tr><td>Stability conditions</td><td>The ZA HA accepts long term stability data generated at either climatic zone II or climatic zone IV conditions. <u>Minimum stability data required at the time of first submission of the registration application – NCE</u>:

Stability information from accelerated and long-term testing is to be provided on at least three batches of the same formulation and dosage form, of the same manufacturing process with API from the API source(s) being applied for, in the containers and closure system proposed for marketing. Pharmaceutical equivalence should be demonstrated for API from different sources. Two of the three batches should be at least pilot scale. The third batch may be smaller (e.g. 25 000 to 50 000 tablets or capsules for solid oral dosage forms). The first three production batches manufactured post-approval, if not submitted in the original application for registration, should be placed on long-term and accelerated stability using the same stability protocols as in the approved application for registration.

<table>
<tr><td></td><td>Storage conditions</td><td>Minimum time period at submission</td></tr>
<tr><td>Long-term testing</td><td>25 ± 2 °C / 60 % ± 5 % RH *</td><td>12 months</td></tr>
<tr><td>Accelerated</td><td>40 ± 2 °C / 75 % ± 5 % RH</td><td>6 months</td></tr>
</table>
* Long-term storage at 30 ± 2 °C/65 % ± 5 % RH or 30 ± 2 °C/75 % ± 5 % RH is also acceptable.</td><td>2.05 Stability Jun10 v5</td></tr>
</table>

<table>
<tr><td>Module No.</td><td rowspan="2">Title</td><td>Standard EU information sufficient
Y/N</td></tr>
<tr><td>Key word</td><td>Source of ZA requirement</td></tr>
<tr><td></td><td><u>Minimum stability data required at the time of first submission of the registration application – generic application</u>:

Stability information from accelerated and long-term testing is to be provided on at least two batches of the same formulation and dosage form, of the same manufacturing process with API from the API source(s) being applied for, in the containers and closure system proposed for marketing. Pharmaceutical equivalence should be demonstrated for API from different sources. One of the two batches should be at least pilot scale. The second batch may be smaller (e.g. 25 000 to 50 000 tablets or capsules for solid oral dosage forms). The first two production batches manufactured post-approval, if not submitted in the original application for registration, should be placed on long-term stability using the same stability protocols as in the approved application for registration.

<table><tr><td></td><td>Storage conditions</td><td>Minimum time period at submission</td></tr><tr><td>Long-term testing</td><td>25 ± 2 °C / 60 % ± 5 % RH *</td><td>9 months</td></tr><tr><td>Accelerated</td><td>40 ± 2 °C / 75 % ± 5 % RH</td><td>3 months</td></tr></table>
* Long-term storage at 30 ± 2 °C/65 % ± 5 % RH or 30 ± 2 °C/75 % ± 5 % RH is also acceptable.</td><td></td></tr>
<tr><td>Assay</td><td>Initial assay results should be expressed as the quantity of API per unit dosage form, in terms of micrograms, milligrams or grams. Assay results for subsequent checkpoints should be given in the same way and as a percentage.</td><td>2.05 Stability Jun10 v5
(pg 13)</td></tr>
<tr><td>3.2.A</td><td>APPENDICES</td><td>-</td></tr>
<tr><td>3.2.A.1</td><td>Facilities and Equipment</td><td>Usually not submitted</td></tr>
<tr><td>3.2.A.2</td><td>Adventitious Agents Safety Evaluation</td><td>Y</td></tr>
<tr><td>3.2.A.3</td><td>Excipients</td><td>Y</td></tr>
<tr><td>3.2.R</td><td>REGIONAL INFORMATION</td><td>As per local requirements</td></tr>
</table>

Module No. Key word	Title	Standard EU information sufficient Y/N Source of ZA requirement
3.2.R.1	**Information and data for multisource applications and NCE line extensions** ***[This module relates to applications which are supported by bioequivalence data]***	-
3.2.R.1.1 – 3.2.R.1.3.1.5 **Bioequivalence studies**	Please refer to the PA CTD guideline (pg 20-26) as the selection of the reference products used for bioequivalence studies must meet specific ZA requirements. If an overseas reference product is used, additional bridging comparative dissolution studies* must be carried out. In addition, specific information tables need to be completed summarising the information about the reference and test products. *[*In the case of topical products (e.g. nasal sprays, metered dose inhalers, multi-dose powder inhalers, etc) alternative equivalence testing would need to be performed,e.g.* • *Studies to demonstrate the in vitro equivalence of the droplet size distribution of the metered dose products, using laser diffraction, spray angle testing.* • *Studies to demonstrate the in vitro equivalence (total drug delivered and fine particle dose) of the metered dose products, using for example the Next Generation Impactor.]*	2.25 PA CTD Jun 10 v1 (pg 20-26)
-	Additional related guideline to be consulted:	2.06 Biostudies Jun 10 v3
-	Additional related guideline to be consulted:	2.07 Dissolution Jun 10 v3
-	Additional related guideline to be consulted:	2.08 Post-reg amendments Jun 10 v4_1
3.2.R.2	**Formal declaration on process – API from different site of the same parent company**	-
API – different site of same parent company	If an identical route of synthesis, or manufacturing process of the PPL (in case of Biological Medicines), including the purification step is used by each site of the same parent company, a statement to this effect must be included in the dossier. In this case valid CoAs from the API manufacturer or manufacturer of the primary production lot (in case of Biological Medicines) for two batches within the retest period at the time of submission of the application issued by each site should be included in 3.2.R.3.3.	2.25 PA CTD Jun 10 v1 (pg 26)
3.2.R.3	**Information and data: API sourced from multiple manufacturers**	-

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
API – different company or route of synthesis	If more than one manufacturer of the API is being applied for (irrespective of the apparent similarity of the routes utilised by the different manufacturers), or when different routes of synthesis are used in the manufacture of the API, the following should be submitted, in addition to Module 3.2.S or 3.2.R.6 for each API:	2.25 PA CTD Jun 10 v1 (pg 27)
3.2.R.3.1	**Comparative API manufacturers study report**	
API –route of synthesis	A report pointing out the differences in the routes used, where applicable, and the differences with regard to the impurity profiles and residual solvents unless justified. The specifications for the API should make provision for these impurities and residual solvents.	2.25 PA CTD Jun 10 v1 (pg 27)
3.2.R.3.2	**Tabulated comparative results from different manufacturing sources of the API**	-
Comparative testing of APIs from different sites	Comparative critical tests, e.g. identification, assay, solubility and/or dissolution, particle size distribution, polymorphism, optical rotation, residual solvents and impurity profiles, to demonstrate physical and chemical equivalence, should be performed on a sample from each API manufacturer. The test must be conducted by the same laboratory (usually either the laboratory of the drug product manufacturer, or an independent laboratory). The same (common) analytical methods and equipment should be used for these tests. These results should be presented also in tabular format and spectra should preferably be overlaid.	2.25 PA CTD Jun 10 v1 (pg 27)
3.2.R.3.3	**Confirmation of compliance with guidelines**	-

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
Local declarations	Confirmation of compliance with the Post-registration Amendments guideline, stating type and category, and identification of the location of the relevant data in the dossier is required. Confirmation of compliance with the Stability guideline (1.2.3 a)) and identification of the relevant data in the dossier is required. ***Although these declarations are signed by the local DRA pharmacist in ZA, there could be implications for further data requirements for the ZA dossier e.g.*** • ***depending on the BCS classification of the API, comparative dissolution in up to 3 dissolution media on the FPP may be required (in cases where the API is sourced from more than one supplier)*** • ***stability data on FPP manufactured with API from all API manufacturers***	2.25 PA CTD Jun 10 v1 (pg 27)
3.2.R.3.4	**Certificates of analysis for each batch of API reported on in 3.2.R.3.2**	2.25 PA CTD Jun 10 v1 (pg 27)
API CoAs	The actual certificates of analysis are required in addition to the comparative table.	2.25 PA CTD Jun 10 v1 (pg 27)
3.2.R.4	**Formal declaration on similarity of process -FPP**	2.25 PA CTD Jun 10 v1 (pg 27)
-	Refer to 3.2.P.3.3 above.	
3.2.R.5	**Medical Device**	**Y – standard EU information sufficient**
3.2.R.6	**Certificate(s) of suitability with respect the Ph.Eur. (CEPs)**	**N**

Module No.	Title	Standard EU information sufficient Y/N
Key word		Source of ZA requirement
Submission of CEP	CEPs may be submitted instead of full API information, however we also need: a) Any information required for the APIF but not addressed in the CEP must be submitted, e.g. physico-chemical properties [3.2.S.1.3 above]. b) If the retest period is not reflected in the CEP, stability data generated according to the Stability guideline and/or supporting literature to demonstrate the API stability should be submitted. (Module 3.2.S.7) c) Certificates of Analysis (CoAs) from the API manufacturer relating to at least two batches within the retest period at the time of submission of the application should be included. (Module 3.2.S.4.4)	2.25 PA CTD Jun 10 v1 (pg 27)
3.2.R.7	**Medicinal products containing or manufactured with materials of animal and/or human origin**	**-**
BSE/TSE-free	All ingredients of animal origin (excluding products from porcine origin) should be declared and specified BSE/TSE free. *[Test to be included in the relevant IPI specification to ensure batch to batch conformance]*.	-
3.2.R.8	**Executed batch records of samples or confirmation that they are available for inspection**	2.25 PA CTD Jun 10 v1 (pg 28)
-	Refer to 3.2.P.3.3 above.	-
3.3	**LITERATURE REFERENCES**	Y
MODULE 4	**NON-CLINICAL STUDY REPORTS**	Y
MODULE 5	**CLINICAL STUDY REPORTS**	Y