

Additional Guidance on Submission Requirements for Medroxyprogesterone Acetate Depot Injection Products Using the Common Technical Document (CTD) format

The World Health Organization's (WHO) invitation to manufacturers of reproductive health products to submit an expression of interest (EOI) for product evaluation to the WHO Prequalification Team. medicines (PQTm) includes 150 mg/ml medroxyprogesterone acetate depot injection in 1 ml vials (henceforth referred to as "DMPA").

Dossiers for generic DMPA products should follow the documentation requirements described in the WHO [Guidelines on submission of documentation for a multisource \(generic\) finished product. Preparation of product dossiers in CTD format](#) (henceforth referred to as "the preparation guideline") published as Annex 15 of WHO TRS 961 (2011) and available on the PQTm website. This additional guidance document is prepared to assist manufacturers in the development of generic DMPA products as well as in the preparation of a CTD dossier for prequalification. Accordingly, this document endeavors to clarify safety/efficacy (bioequivalence (BE)) and quality requirements for generic DMPA injection and provide examples as well as recommendations where appropriate. Since this document is not a stand-alone guideline, it should be used in conjunction with the main safety/efficacy and quality guidelines issued by PQTm for submission of documentation for prequalification.

MODULE 1

Refer to the preparation guideline.

Section 1.3

Draft Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labels should be included as prepared using the format provided on the PQTm website (under WHO Public Assessment Reports).

The product information can be drafted based on the comparator product information and should reflect particulars specific to the proposed formulation where relevant (e.g. extent of shaking required to re-suspend the product prior to administration). The draft product information will then be finalized as part of the WHOPAR preparation that normally follows prequalification.

Section 1.4/1.5

A properly completed Bioequivalence Trial Information Form (BTIF) in MS Word format should be included.

For the quality part, a properly completed Quality Overall Summary - Product Dossier (QOS-PD) and Quality Information Summary (QIS) templates in MS Word format should be included.

The latest versions of the QOS-PD and QIS templates are available on the PQTm website, under Documents A–Z.

Section 1.6

For applications to PQTm, PQTm has identified comparator products that should be used in bioequivalence studies. The comparator products are listed on the PQTm website under Key Resources, Procedures and Fees for WHO Prequalification, Full Assessment, Bioequivalence.

Comparator products should be purchased from a well-regulated market with a stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonisation (ICH), i.e. European Union, Japan, USA, Canada, Switzerland and other countries associated with ICH (through legally binding mutual recognition agreements) including Australia, Norway, Iceland and Liechtenstein. In the case where the WHO

recommended comparator product cannot be located in a well-regulated market with a stringent regulatory authority as noted above, the applicant should consult WHO regarding the choice of comparator prior to initiating any studies.

Certificates of analysis should be included for the biobatch of the proposed product and the relevant batch of the comparator product, analysed at a time near the time of the BE study.

The following information related to the comparator product should also be included:

1. A copy of the comparator product labelling: the name of the product, name and address of the manufacturer, batch number and expiry date should be clearly legible on the labelling.
2. A copy of the invoice from the distributor or company from which the comparator product was purchased: the address of the distributor should be clearly legible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market: the certification should be signed by the company executive responsible for the application to PQTm.

Section 1.7

A sample of the product as packaged for marketing should be provided.

MODULE 2

Refer to the preparation guideline.

A hard copy of the QOS-PD should be included, as well as reference to the electronic copy of the QOS-PD in Module 1.5.

For the safety/efficacy part, Modules 2.4-2.7 of the CTD need not be completed if the BTIF is completed for dossiers that rely solely on pivotal bioequivalence studies to establish safety and efficacy.

MODULE 3

Refer to Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for WHO prequalification: quality part (WHO TRS 970, Annex 4), available on the PQTm website. Henceforth, this guideline is referred to as “the generic guide”.

3.2.S Drug substance (active pharmaceutical ingredient)

Refer to section 3.2.S of the generic guide. Active pharmaceutical ingredients (API) prequalification, certification of suitability (CEP of the European Directorate for the Quality of Medicines) and/or the API master file (APIMF) procedures are the preferred options for submitting the API information.

3.2.S.1 General information

Refer to section 3.2.S.1 of the generic guide and to discussion provided below in section 3.2.P.2.

3.2.S.2 Manufacture

Refer to section 3.2.S.2 of the generic guide.

Where the API is claimed to be sterile:

A complete description of the aseptic processing and/or sterilization methods should be provided. In addition, validation data for the sterilization of API, packaging components and critical manufacturing equipment should be included in the application.

Where sterilizing filters are employed to render the API sterile, compatibility of the API with the filters should be demonstrated. Results from a recent media fill study should also be provided if aseptic processing is the method of choice.

Where the API is sterilized by irradiation, the bioburden of the API prior to irradiation should be controlled. The validation and control of the irradiation process should take into account the recommendations in ISO 11137 — Sterilization of health care products — Radiation. There should be a valid good manufacturing practices (GMP) contract with the irradiation site.

A description of the controls used to maintain the sterility of the API during storage and transportation should be provided.

3.2.S.3 Characterization

Refer to section 3.2.S.3 of the generic guide.

The results of an investigation of the polymorphic form(s) of the API produced from the proposed manufacturing process should be provided. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specifications to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability studies. Where the API is micronized, the polymorphism test should be applied after the micronization process. The polymorphic characterization by XRPD should be provided of the API batch(es) used in comparative bioavailability studies. The method used to control polymorphic form should be demonstrated to be specific for the preferred form. For further guidance refer to 3.2.S.3.1 of the generic guide under the section entitled, “*Polymorphism*”.

As discussed later in section 3.2.P.2, particle size is a critical quality attribute (CQA). In this regard, the particle size distribution (PSD) of the API lot used to manufacture the biobatch should be established and the data should be used to set limits for routine control of the API (limits for d10 (< x), d50 (as a range) and d90 (< y) should be included). Additional limits for d95 and/or d99 may also be appropriate.

The impurity limits should be established in line with recommendations of ICH Q3A. In general, where linear release is established, the maximum daily dose may be calculated as the total quantity of API divided by the duration of release. However, if a product exhibits a burst effect as in the case of DMPA, or other non-linear release, the maximum amount released over 24 hours should be considered the maximum daily dose. Identification and qualification thresholds should then be defined accordingly using ICH Q3A principles.

3.2.S.4 Control of the API

Refer to section 3.2.S.4 of the generic guide.

When the prequalified API (API PQ) or APIMF option is utilized, the API specification proposed by the finished pharmaceutical product (FPP) manufacturer should incorporate all the tests included in the API PQ or APIMF accepted specification, respectively. When the CEP option is used, the API specifications should include all the tests and limits of the CEP and European Pharmacopoeia (Ph. Eur.) monograph. Regardless of the option used, additional in-house tests for PSD, polymorphism, sterility and bacterial endotoxin test (BET) should be included as applicable.

Since PSD is considered to be an important API quality parameter, the analytical method for the PSD test should be validated for accuracy and precision. The other analytical methods, including sterility and BET methods, should also be validated or verified as applicable.

3.2.S.5 Reference standards or materials

Refer to section 3.2.S.5 of the generic guide.

3.2.S.6 Container closure system

Refer to section 3.2.S.6 of the generic guide.

The applicant should demonstrate the suitability of the proposed container closure system for use with the API. For a sterile API, the applicant should also discuss the sealing design and provide one-time data to demonstrate the integrity of the container closure system by either a microbial or dye ingress test. In addition, evidence should be submitted that the selected mode of transportation does not compromise the sterility of the API. This is typically addressed by container integrity testing of filled and sealed containers that were subjected to the actual or simulated transportation conditions. Samples should also be tested for physicochemical tests. A copy of the standard operating procedure (SOP) used for receiving sterile API at the FPP site should be submitted with the application.

Aseptic sampling of sterile bulk API before dispensing for use in the manufacture of the FPP introduces an avoidable risk to sterility. For sterile APIs, sampling at the point of dispensing should be considered. Most companies producing sterile APIs will also provide side sample(s) for the FPP site to perform release testing. In the case where side sample(s) are provided by the supplier, the method and validation of sampling, sample size and its packaging must be initially assessed and agreed with the supplier (in the technical/supply agreement) and thereafter re-evaluated periodically. This supporting information should be maintained at the site but need not be submitted for assessment.

3.2.S.7 Stability

Refer to section 3.2.S.7 of the generic guide.

Where the API is supported by a CEP and the CEP does not specify the storage conditions and retest period, stability data should be provided to support the proposed retest period and storage conditions. It should be noted that the required long-term storage conditions for APIs in PQTm are either $30\text{oC} \pm 2\text{oC}/65\% \pm 5\% \text{RH}$ or $30\text{oC} \pm 2\text{oC}/75\% \pm 5\% \text{RH}$.

When the CEP indicates a retest period without a storage condition, or indicates storage below 25°C , data should be provided to either support storage below 30°C or to demonstrate the unsuitability of this storage condition for the API. If this data is unavailable, a commitment to submit this data for two pilot lots is required.

Since PSD is a CQA, the test should be included as a parameter during stability studies and retesting. Where the API is supported by a CEP or the data was not included in the APIMF, the proposed retest period should be substantiated by additional stability results with respect to PSD of the API.

3.2.P Finished pharmaceutical product (FPP)

3.2.P.1 Description and composition of the FPP

Refer to section 3.2.P.1 of the generic guide.

3.2.P.2 Pharmaceutical development

Refer to section 3.2.P.2 of the generic guide.

DMPA is a sterile suspension of medroxyprogesterone acetate (MPA) in aqueous medium. It is a long-acting contraceptive agent to be administered by deep intramuscular injection as described in the comparator SmPC/PIL. According to the EOI, 1 ml of the depot injection presented in a vial is invited, implying single use.

The aim of the development programme is to obtain a stable injectable suspension bioequivalent to the WHO comparator product Depo-Provera® 150 mg/ml of Pharmacia/Pfizer Limited. Thus the composition and the physical properties of the vehicle and the solid state properties of the API should be carefully considered during development.

It is of critical importance that the in vivo properties remain unchanged during the life-cycle of the product. Accordingly, the in vitro release properties of the biobatch should be retained in commercial batches, at release and during the shelf life. Therefore the specifications (release and shelf life) should include discriminating test(s) for monitoring the release of the API from the formulation. See the further discussion in 3.2.P.2.2.1.

The review article by R.M. Patel: *Parenteral suspension: An overview* published in *International Journal of Current Pharmaceutical Research*, Vol. 2, Issue 3, pp. 4–13, 2010 is recommended for reference. The ideal characteristics of parental suspensions are defined as follows:

- The suspensions are manufactured and tested for microbial contamination, in order to maintain its sterility during its storage and use.
- It should be easily drawn into a syringe (syringeability) and readily ejected from the syringe (injectability). The syringeability and injectability of a suspension are closely related to viscosity and particle characteristics.
- Particle size should be small and should be uniform within the dosage unit, between doses and between batches.
- Re-suspension of drug particles should occur easily with mild shaking.
- The dispersed particles do not settle rapidly after shaking.
- Re-suspension should result in homogeneous mixing of drug particles in such a manner that the same concentration of drug can be removed repeatedly.
- Cake formation should not occur during its shelf life.
- The suspension should maintain its stability and elegance during its shelf life.
- It should be isotonic and non-irritating.

These characteristics should be dealt with satisfactorily in the different sections of development of generic DMPA, below.

3.2.P.2.1.1 Active pharmaceutical ingredient

Refer to section 3.2.P.2.1.1 of the generic guide.

Compatibility of the API with the selected excipients should be demonstrated as indicated in 3.2.P.2.1.1 of the generic guide. In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate API–excipient compatibility. Demonstration of API–excipient compatibility is not required for excipients that are present in the comparator product. The qualitative list of excipients in Depo-Provera can be found in section 6.5 of the SmPC (EU) and in the product information (U.S.) for products in the respective regions.

The solubility of the API is important for a suspension. The solubility in aqueous medium over the pH range 1.2 to 6.8 at 37°C should be determined and provided in the dossier. Since the structure of MPA contains no acidic or basic groups it is expected that the pH will not have a significant effect on its solubility in aqueous medium.

The solid state properties of the API are considered CQAs for product performance and the following should be considered during development:

- Particle size distribution (PSD)
- Crystal modification (polymorphism)
- Other properties that can influence the product with respect to e.g. manufacturability and stability (hygroscopicity, melting point, etc.)

The importance of the solid state properties of MPA in the DMPA injection is well established as illustrated by the following publications:

O'Neil stated in his Master's thesis, Northeastern University: "Controlling drug delivery for the application of extended or sustained-release drug products for parenteral administration" that "Microcrystalline

- particles, commonly used with depot injections of an active drug, help to control the release of the drug to the surrounding tissue. Depending on the size of particles used, dissolution rates may increase (for smaller particles), or decrease (with larger particles). It is known that micronized MPA is used in the formulation of DMPA.”
- In the Handbook of Pharmaceutical Controlled Release Technology (Donald L. Wise, Ed) it is mentioned that “because Depo-Provera is formulated as an aqueous microcrystalline suspension, there can be major differences in the particle size distribution despite their being “micronized”. The steroid can exist in several polymorphic forms which can influence the structure and hence the hardness of the crystals being micronized. Furthermore the micronization process can be undertaken in several ways. Thus, very different PSDs can be obtained in which Depo-Provera preparations can be claimed to be micronized.”
- In Hall, PE (1987), Long-acting injectable formulations; Fertility Regulation Today and Tomorrow. Eds. Diczfalusy, E & Bygdeman, M. Serono Symposia, vol 36, pp119-141. Raven Press, New York, the following is reported: “The Task Force on Long-Acting Systemic Agents continues to investigate the association of particle size of microcrystalline suspension, such as Depo-Provera, and duration of action. It is postulated that at least in certain populations, such as in Thailand, formulations comprised of predominantly small particles (less than 10 µm) permit more rapid absorption and elimination of MPA than formulations with particles of a broader size range.”

The PSD of the API material is of critical importance for the extended in vivo performance of DMPA preparations. The API should be micronized to consistent, uniform PSD (see also Patel as quoted in 3.2.P.2). The PSD of the API batch used in the FPP biobatch should be characterized and used for setting the PSD limits in the API specifications (see 3.2.S.3 above). PSD should also be included in API stability testing to ensure that no change is observed on storage, i.e. that the PSD will always be the same when used in the manufacture of the FPP. The milling/micronization process should also be described and validated, including a demonstration that the process does not affect the polymorphic composition or crystalline nature of the API. Particle size measurements should be done using a validated method on a particular apparatus, preferably by laser diffraction. Different methods/instruments may give different results; therefore it is important to have a single dedicated method for all PSD testing. Data provided in 3.2.S should be summarized and discussed here.

Where API suppliers are proposed in addition to the supplier of the API biobatch, PSD should form part of the comparative studies using the same apparatus and validated test conditions for batches from each supplier, including the API biobatch. Comparative data should also be provided on the PSD of batches of the FPP manufactured using API from all proposed suppliers.

Information on the polymorphic behaviour of MPA is required (see above in 3.2.S.3). At minimum it should be demonstrated that the crystal form of the API as supplied by the API manufacturer remains unchanged, batch to batch, compared to the lot used in the bioequivalence studies. Where the API is micronized, the polymorphism test should be applied after the micronization process. Such evidence could have been discussed in section 3.2.S.3 in which case reference to this section may suffice. XRPD in particular is suitable for identification of the polymorphism, though IR and DSC could suffice if suitably validated. If the API is obtained from more than one API manufacturer, the same polymorphic form must be demonstrated for material from each manufacturer.

3.2.P.2.1.2 Excipients

Refer to section 3.2.P.2.1.2 of the generic guide.

The choice of excipients listed in 3.2.P.1, their concentration and their characteristics that can influence the FPP performance should be discussed relative to their respective functions.

According to Patel, “parenteral suspensions limit the formulator in selecting the ingredients, which are parenterally acceptable as suspending agent, viscosity inducing agent, wetting agent, stabilizers and [for multi-dose injectables] preservative.” The article indicates the difficulties of selection of the excipients and

their concentrations and states inter alia, “The tendency for crystal growth in a suspension can be diminished by using a narrow particle size range, decreasing interfacial tension (to reduce the free energy of particle), increasing the viscosity of suspending medium (may be difficult with parenteral suspensions as it affects the syringeability and flow), use of hydrophilic gums like polyvinylpyrrolidone, polysorbates (adsorb at particle surface and retard crystal growth)...”

In the comparator product, PEG 3350 is used as viscosity and suspending agent, sodium chloride is used as tonicity agent and polysorbate 80 is used both as surfactant and to reduce the tendency of crystal growth. The concentrations are available in the U.S. product information for Depo-Provera CI. See 3.2.P.2.2.1 for more details.

3.2.P.2.2.1 Formulation development

Refer to section 3.2.P.2.2.1 of the generic guide.

The quality target product profile (QTPP) and CQAs of the FPP should be defined in relation to the dosage form, administration route and comparator product. The main CQAs with respect to the in vivo performance are:

- The viscosity and tonicity of the suspension. These can affect the distribution (absorption area) in the muscle tissue upon injection, which in turn can have an effect on the rate of in vivo absorption;
 - The PSD of the suspended API; and,
 - The dissolution characteristics of the suspension.

As indicated in 3.2.P.2.1.2, viscosity and PSD also affect the physical properties (syringeability, resuspendability, etc.) of the suspension. To handle the rather complex situation in targeting the QTPP of the comparator, a first approach would be adoption of the composition of the comparator product. The quantitative composition of Depo-Provera CI is available in the U.S. product information:

Each ml contains:

Medroxyprogesterone acetate	150 mg
Polyethylene glycol 3350	28.9 mg
Polysorbate 80	2.41 mg
Sodium chloride	8.68 mg
Methylparaben	1.37 mg
Propylparaben	0.150 mg
Water for injection	quantity sufficient

When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid.

In vivo performance testing

One or preferably more batches of the comparator product should be analysed. Target the performance characteristics by conducting the following tests:

- Viscosity
- PSD
- Dissolution

Particle size measurements should be done using a validated method on a particular apparatus, preferably by laser diffraction. Different methods/instruments may give different results; for comparative purposes it is important to have a single dedicated method for all PSD testing regardless of the product or sample tested.

A discriminatory dissolution method should be developed. USFDA Recommended Dissolution Methods may be used as the starting point in developing a method that is suitable for the proposed product.

Two methods are recommended by USFDA, namely Test 1 (apparatus IV, flow through cell) and Test 2 (apparatus II, paddle).

Parameters such as the dissolution medium (surfactant concentration), flow rate, paddle speed and sampling times should be optimized to obtain discriminative profiles. The discrimination power should be tested in relation to PSD (varying particle size, keeping other parameters constant) and viscosity (varying macrogol (PEG) grade/quantity while keeping other parameters constant). For tests on the generic product, lab batches need not be sterile.

Alternatively, once these studies are published, reference may be made to the Concept Foundation studies on apparatus IV and II. Additional studies using either apparatus may also be undertaken to develop a suitable method for routine control of the proposed product. As noted below, the presence of a suitable release method can be supportive of post-prequalification variations.

The FPP specifications (release and shelf life) are to be set using the results obtained for the generic biobatch. One or both methods (apparatus II or IV) should be selected for dissolution testing, depending on their discriminating power.

It is imperative that the critical characteristics, including resuspendability, content uniformity, viscosity, PSD and dissolution rate (when applicable), remain unchanged during the product's life-cycle in order to ensure retention of in vivo performance.

As noted, suitable development work should be undertaken to find a meaningful release rate method for the proposed product using both the paddle and FTC apparatus. In the event that it is concluded that a release-rate test appropriate to the product cannot be established (e.g. by reference to the published Concept Foundation studies and/or additional studies), the following elements may as a whole be used to justify the exclusion of a release rate test as a quality parameter:

- A comprehensive summary of the release rate development work as above

- Adequate characterization and control of PSD in API and FPP specifications, and of polymorphism if relevant

- Adequate characterization and/or control of redispersion (resuspendability) (D), syringeability (D), vehicle viscosity (in-process), and solubility of API in the vehicle (in-process). (D = development data).

Control of the parameters above should include suitable raw material specifications and in-process controls during the manufacturing process.

A demonstration should be provided to show consistency between production batches and the biobatch(es) with respect to the above parameters.

Batch release data should demonstrate that the process is well controlled and that the overall variability is low.

It is critical to note that in the absence of a release rate method in the finished product specifications, any changes to the product formulation, manufacturing process or PSD (API or FPP) will necessitate the need for an additional bioequivalence study.

3.2.P.2.2.2 Overages

Refer to section 3.2.P.2.2.2 of the generic guide.

An overage may be used when justified in terms of loss during manufacture of the product as indicated in the generic guide, section 3.2.P.2.2.2. No overage of the API is expected, since it is introduced (as sterile material) in the solid state.

If sterilization of the solution(s) that contain excipients is accomplished via filtration, loss of excipients present in the formulation in relatively small quantities should be investigated, e.g. sodium chloride used in the formulation to set tonicity.

Overfilling of the vial is required to ensure correct dose administration. Data must be collected to calculate and justify the overfill volume.

3.2.P.2.2.3 Physiological and Biological Properties

Refer to section 3.2.P.2.2.3 of the generic guide.

The proposed formulation should be characterized for re-suspendability, syringeability and injectability as well as sedimentation rate.

Sedimentation rate may be evaluated by comparing sedimentation volume measured right after shaking (as instructed in the SmPC) and at the end of a reasonable period of time which may elapse during dose preparation and administration to the individual.

Re-suspendability may be demonstrated by reporting the relative shaking effort required to achieve a homogenous suspension as visually determined (re-suspendability with minimal effort, mild or vigorous shaking). The SmPC should then reflect the level of shaking required to achieve a homogenous suspension. Formulations that require vigorous shaking for re-dispersion should be carefully evaluated as the action of vigorous shaking may also lead to increased solubility.

Syringeability and resuspendability should be demonstrated via determination of uniformity of dosage units (i.e. by analyzing content of the vials as withdrawn following the procedure described in the SmPC). In this case, the samples should be withdrawn using common syringe and needle types used for administration of DMPA injection, including the type(s) used in the bioequivalence study. Syringes with 21–23 gauges appear to be commonly used devices for administration of DMPA injection. Syringeability and injectability characterization may be supported by demonstrating similarity in viscosity, particle shape and PSD profile with the comparator product.

The proposed formulation should also be tested for viscosity at 37°C on a one-time basis. The viscosity data may then serve as a reference for future comparisons to support certain changes.

3.2.P.2.3 Manufacturing process development

Refer to section 3.2.P.2.3 of the generic guide.

Due to stability concerns, most DMPA products appear to be manufactured by aseptic processing. However, it is also our understanding that one or more manufacturers may be employing terminal sterilization processes. If terminal sterilization is used, the applicant is expected to provide a specific discussion as to stability of the product in terms of degradation products, PSD growth, crystal modification and performance parameters (re-suspendability and release characteristics).

For products manufactured by aseptic processing, data should be submitted on filter validation (integrity, compatibility, extractables/leachables and bacterial retention efficacy) in relation to the proposed vehicle system. As the filter suppliers are in a better position to perform the study, it is recognized that such studies could be contracted out to the filter supplier. For products that contain hydroxybenzoates which may interfere with the filter validation studies, a simulating vehicle without the hydroxybenzoates may be used.

3.2.P.2.4 Container closure system

Refer to section 3.2.P.2.4 of the generic guide.

Glass vials should meet the United States Pharmacopeia (USP) <660> requirements or equivalent.

Rubber stoppers should meet USP <381> including requirements described in USP <87>/<88>. In addition, the composition of the rubber stopper should be provided with a declaration that the material is free from 2-mercaptobenzothiazole

(MBT) and nitrosamines (as obtained from the rubber supplier). Furthermore, data on the extractables profile of the proposed rubber stopper as well as leachables data as tested with sensitive analytical methods should be provided. Silicon oil used for siliconization of rubber stoppers should be of pharmacopoeial grade and the specification should be provided as part of section 3.2.P.7.

3.2.P.2.5 Microbiological attributes

Refer to section 3.2.P.2.5 of the generic guide.

Container integrity should be demonstrated, preferably via the microbial ingress test, however the dye ingress test is acceptable if justified. We recommend that the study be performed as part of medial fill runs.

Although the product is presented as a single dose, the comparator product contains hydroxybenzoates and it is possible that the generic products will be formulated accordingly. According to AusPAR for Sayana SC injection (a similar product formulated with all excipients in Depo-Provera, as well as other excipients), these are used as re-suspending agents. Where the hydroxybenzoates in the generic DMPA are qualitatively and quantitatively in agreement (Q&Q) with those in the comparator product (Depo-Provera), no further information or data is considered necessary to justify inclusion of these excipients in the proposed formulation. Applicants are discouraged from having differences in Q&Q, which could be considered unacceptable or lead to additional supportive data requirements, depending on the differences.

3.2.P.2.6 Compatibility

Not applicable.

3.2.P.3 Manufacture

Refer to section 3.2.P.3 of the generic guide.

The process flow chart and narrative description should identify the area classification and environmental controls maintained during each step of the manufacture.

The blank master record (BMR) or referenced SOPs should identify validated equipment and process parameters. For example, an SOP or a section of the BMR that refers to depyrogenation of glass vials via tunnel depyrogenator should specify the validated sterilization parameters (depyrogenation temperature in the hot zone, conveyer speed, dwell time and air velocity in each of the drying, depyrogenating and cooling zones). In this regard, copies of all key SOPs referred to in the BMR should be provided as part of section 3.2.P.3.3 of the dossier or as annexures to the blank BMR.

In-process controls performed during vehicle preparation and sterilization, suspension preparation, filling and sealing should be described in the BMR or the BMR should refer to the SOPs and copies of the SOPs should be provided. The following in-process tests should be considered:

- The bioburden should be determined immediately prior to final sterilizing filtration (total viable count (TVC) of NMT (not more than) 10 CFU/100 ml). Such low bioburden may be assured by limit testing in the case of a single filtration step or serial filtration with the monitoring of the bioburden earlier in the process
- the integrity of filters should be confirmed before and after filtration and results should be recorded in the batch manufacturing records
- the bacterial endotoxin level of the vehicle system before filtration should be controlled and periodically monitored
- the sterile bulk vehicle should be sampled and tested for visible particles and for the solubility of the API
- vials sampled during filling and sealing should be tested for absence of contaminating particulate/foreign matters
- leak testing of the filled and sealed containers should be conducted using a validated method.

Details of environmental monitoring (e.g. particle count and microbiological examination of air and surfaces, pressure differentials across adjacent areas, air change rate and velocity) in all critical areas should be described in BMR or in referenced SOPs.

Hold times for sterilized equipment, accessories and container components should be validated and should normally not exceed 48 hours.

For an aseptically processed FPP, sterile filtration of the bulk vehicle, preparation of the suspension and filling of the formulated suspension into final containers should preferably be continuous. Any holding time prior to sterile filtration should be justified with supportive stability data (at minimum appearance, pH, bioburden and resuspendability).

3.2.P.3.5 Process validation

Refer to section 3.2.P.3.5 of the generic guide.

The dossier should include the following process validation data:

- Depyrogenation of the glass vials from three consecutive runs (demonstration of heat distribution, heat penetration and depyrogenation efficacy)
- Washing of rubber stoppers and seals
- Sterilization of accessories, rubber stoppers and seals (heat distribution and heat penetration data as well as microbiological efficacy of the sterilization cycle at the scale and load pattern proposed for production batches)
- Product sterilization (filter validation for aseptically manufactured products; heat distribution data, heat penetration data and microbiological efficacy data for terminally sterilized products)
- Recent media fill validation data (for products manufactured by aseptic processing); the study should be appropriately designed to ensure the process is validated for the proposed product
- Vehicle preparation, homogenization, filling and sealing (on three consecutive production batches of the product)
- A demonstration of homogeneity of the suspension throughout storage and filling (including interruptions).

3.2.P.4 Control of excipients

Refer to section 3.2.P.4 of the generic guide.

Specification for excipients should include a test for bioload or bacterial endotoxins. A limit for TVC of NMT 10 CFU/g is recommended.

If nitrogen purging is applied, the gas should be passed through sterilizing grade filters (i.e. gas should be sterile).

3.2.P.5 Control of FPP

Refer to section 3.2.P.5 of the generic guide.

Refer to monographs for MPA injection in officially recognized pharmacopoeia, i.e. British Pharmacopoeia (BP), International Pharmacopoeia (Ph. Int.), Ph. Eur., Japanese Pharmacopoeia and USP.

The proposed specification, regardless of whether in-house or pharmacopoeial standard, should include all tests cited in the specific official monographs as well as additional tests for description, pH, specific gravity, extractable volume, PSD, uniformity of dosage units, dissolution (when applicable), sterility, bacterial endotoxins (with a limit of NMT 2.3 EU/mg of MPA) and electrolyte content. If hydroxybenzoates are used, the specification should also include a test for identification and assay of the hydroxybenzoate(s). A test for sodium chloride content (used as tonicity agent) should also be included.

The sample preparation description in the test for content uniformity should describe the withdrawal of product from the vials following the procedure outlined in the SmPC.

The routine test and limit for dissolution should be set based on the dissolution characterization performed as part of the development studies, as described above.

Tests and limits for degradation products should be set as per ICH Q3B. A report should be provided discussing all possible MPA degradants and including an investigation of all related compounds identified in the available officially recognized pharmacopoeial monographs for the FPP.

All potential degradants should be controlled in the specifications as per the principles of Q3B and the limits for specified related substances should be suitably qualified. Note that pharmacopoeial limits for specified related substances are considered qualified. The limit for individual unspecified related substances should correspond to the identification threshold based on the maximum daily dose as discussed in 2.3.S.3.

It is recommended that the thin layer chromatography (TLC) test for impurity F and the high performance liquid chromatography (HPLC) test for other related substances described in the BP and Ph.Int. monographs be adopted in which case the methods need only be verified (separation at the limit of detection (TLC) and specificity, repeatability and accuracy (HPLC)) and validated for any specified related substances beyond those identified in the monographs. In-house methods should be fully validated.

Similarly, the assay method described in USP, BP or Ph.Int. monographs may be adopted when supported with method verification data (specificity, repeatability and accuracy).

Limits for PSD should be set as described for the API above. The analytical method should be validated in relation to the specific formulation.

Evidence of validation should be provided for tests for bacterial endotoxin and sterility.

3.2.P.6 Justification of specification(s)

Refer to section 3.2.P.6 of the generic guide.

3.2.P.7 Container closure system

Refer to section 3.2.P.7 of the generic guide and the discussion provided above in section 3.2.P.2.4.

Section 3.2.P.8 Stability

Refer to section 3.2.P.8 of the generic guide.

It should be noted that the required long-term storage conditions for FPPs in PQTm is $30\text{oC} \pm 2\text{oC}/75\% \pm 5\%$ RH, however the humidity condition is not required for storage in glass vials.

Stability studies should include data on vials stored in inverted positions.

The parameters monitored during stability studies should include description, pH, re-suspendability, assay, degradation products, PSD, dissolution (when applicable), specific gravity (as relevant), hydroxybenzoate(s) content (if used), sterility (at initial and final time points) and any other parameter(s) determined to be stability-indicating. For example, content uniformity should be demonstrated for this product in the primary stability studies.

Regardless of the storage instructions, the physical stability of the product should be demonstrated during freeze-thaw studies, and should include tests for description, assay, degradation products, dissolution (when applicable), sterility, PSD and any other parameter(s) determined to be stability-indicating.

The storage statement for the product should include "Do not freeze".

3.2.R Regional Information

Refer to section 3.2.R of the generic guide and the discussion above in section 3.2.P.3.3.

MODULE 4

If the dossier relies solely on pivotal bioequivalence studies to establish safety and efficacy, Module 4 of the CTD is not generally applicable.

MODULE 5

5.3.1.2 - Comparative BA and bioequivalence (BE) study reports

Since the formulation under consideration is an injection which releases MPA in a prolonged fashion, MPA has a long (apparent) elimination half-life, and the formulation is administered once every three (3) months, a cross-over study does not seem feasible. A parallel design is considered the best option. With regard to this parallel study, careful attention should be paid to the distribution of patients in the two different groups of treatment to prevent imbalance (e.g. poor or extensive metabolizers, weight and age).

A randomized, single dose, parallel design bioequivalence study should be undertaken for 140 days post-injection. A single 150 mg dose of the test formulation or the comparator formulation should be administered following the posology in the product labeling. As such, the comparator product should be administered with a 22-gauge x 1.5 inch needle. It is recommended that the same gauge needle be employed for the test product. If a different size needle is employed for the test formulation, its use should be justified and the gauge of that needle should be specified in the posology in the proposed product labeling. Based on published data of the USFDA from an Abbreviated New Drug Application, the number of subjects to be included should be at least 70 per arm. In addition, additional subjects should be included to compensate for possible dropouts. However, the decision regarding the number of subjects to be included in the study is the responsibility of the applicant.

Blood sampling needs to be undertaken up to 140 days after the day of injection. The following sampling scheme is suggested: pre-injection, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 16, 18, 21, 24, 28, 35, 49, 63, 77, 90, 105, 119 and 140 days. As such, blood sampling covers the MPA concentration-time curve over the administration period of every three months (91 days) and the elimination phase after this period.

For this single-dose bioequivalence study of a prolonged release formulation, the following parameters should be measured or calculated:

- C_{max}
- AUC(0-90days)
- AUC(0-140days)
- AUC(0-infinity)
- AUC(0-21days)
- AUC(21-49days)
- AUC(49-90days)
- T_{max}
- T_½

AUC(0–90days), AUC(0–140days) and C_{max} are the pivotal parameters for which bioequivalence should be proven. The other parameters listed above are considered supportive data.

With regard to the statistical considerations, the data for MPA should meet the following bioequivalence standards:

- The 90% confidence interval of the relative mean of AUC(0-90days) of the test to comparator product should be within 80–125%.
- The 90% confidence interval of the relative mean of AUC(0-140days) of the test to comparator product should be within 80–125%.
- The 90% confidence interval of the relative mean of C_{max} of the Test to comparator product should be within 80–125%.

Clinical study reports, including bioequivalence study reports, are to be structured in accordance with ICH E3: *Structure and Content of Clinical Study Reports*.

This section of the submission should include a detailed description of each study performed to establish the relative bioavailability and therefore, bioequivalence of each formulation. The reports should be based on raw quantitative and qualitative data and will require the compilation of summary tables and graphs.

The clinical study report must include factual and concise descriptions of the methods and materials used, presentation of the results and critical evaluation of the study design, analytical methodology and statistical analysis of data. It should be presented in sufficient detail to allow an independent evaluation of the drug. It is important that the bioequivalence report state, clearly and unambiguously, the chemical and pharmaceutical formulations used in the study of the drug.

Detailed accounts of, and reasons for, all protocol modifications, deviations, or violations must be highlighted, explained and cross-referenced to the original study protocol.

Generally, it is unlikely the clinical study report for a bioequivalence trial will include all of the sections outlined in the ICH E3 guidance document. It is anticipated that some specific issues within various sections will not be applicable. For example, within section 11.4 (Efficacy Results and Tabulations of Individual Patient Data), it is unlikely that the following sections will be applicable.

Section 11.4.2

Section 11.4.2.1 Adjustments of Covariates

Section 11.4.2.3 Interim Analyses and Data Monitoring

Section 11.4.2.4 Multicentre Studies

Section 11.4.2.5 Multiple Comparison / Multiplicity

Section 11.4.2.6 Use of an "Efficacy Subset" of Patients

Section 11.4.2.7 Active-Control Studies Intended to Show Equivalence

Section 11.4.2.8 Examination of Subgroups

However, section 11.4.2.2 (Handling of Dropouts or Missing Data) and 11.4.7 (Efficacy Conclusions) will be applicable and should be addressed.

Sections of the clinical study report (E3) that are not applicable should appear in the table of contents for the clinical study report with the words "not applicable"; however, it is not necessary to include tabs for these non-applicable sections in the body of the report. If the table of contents for Module 5 of the dossier identifies the sections of the clinical study report (E3), sections that are "not applicable" should be handled in the same manner as described for the table of contents for the report.

5.3.1.4 - Reports of bioanalytical and analytical methods for human studies

Reference to the various bioanalytical method validation guidelines should be made here.

The analytical part of bioequivalence trials should be performed in accordance with the principles of Good Laboratory Practice. Prior to beginning the bioequivalence study, the analytical method should have been validated and proven to be accurate and precise for analysis of MPA over the range of concentrations anticipated.

For validation, specificity, accuracy, precision, the lower limit of quantitation, the response function (calibration curve performance) and stability of MPA under the designated storage conditions have to be demonstrated. Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol, and/or the SOP. Normally for a crossover study, the lower limit of quantitation of the bioanalytical method should be 5% of C_{max} or lower, since this is the level at which pre-dose concentrations should be detectable. However, as this is a parallel design study, the lower limit of quantitation should be sufficiently low to measure accurately and precisely the MPA plasma concentrations, not only during the first

90 days after injections, but also over the following days up to 140 days after administration, for a reliable estimation of the elimination phase and thus AUC(0–infinity).

All experiments used to support claims or draw conclusions about the validity of the method should be described in a method validation report that is included in the submission to PQTm.

During analysis of subject samples, within study validation should be carried out using quality control samples in each analytical run. Acceptance criteria should be predetermined and in accordance with normally applied criteria. Reanalysis of subject samples should be defined in the study protocol and/or SOP. Normally, reanalysis of subject samples for pharmacokinetic reasons is not acceptable. This is especially important for bioequivalence studies, as this may bias the outcome of such a study. Incurred sample re-analysis studies should be conducted.