APPENDIX 30

CHANGE OF MANUFACTURING SITES (COS)

Change of Manufacturing Site (COS) refers to change of manufacturing site for certain or all of the manufacturing process of a product. This does not cover changes related to a new site, where **only**:

a) batch release takes place OR

b) primary or secondary packaging including labelling takes place, as these changes are covered under applications for amendments to the particulars of a registered product

However, a change of manufacturing site for biologics shall require a new product registration if the change is extensive and will have an impact on the quality, safety and efficacy profile of the final product.

Once NPRA deems the application is complete, the outcome of the COS application shall be decided by the Drug Control Authority (DCA) within sixty (60) working days.

1. CONDITIONS ON APPLICATION FOR COS:

COS is only applicable for the following situations:

a) a change in manufacturing site for the same company, including rationalization in the event of mergers; or

b) a company that previously contracts out the manufacture of its product(s) transfers the manufacture of the product to its own manufacturing premises; or

c) a company appoints a contract manufacturer (in or outside Malaysia) for the following product categories:

   i. new drug products
   ii. biologics
   iii. generic products containing scheduled and non-scheduled poisons
   iv. veterinary products

d) a company appoints a contract manufacturer in Malaysia for health supplement products. This change includes a change from a contract manufacturer to a local contract manufacturer or a change from own manufacturing premise to a local contract manufacturer, or

e) crisis situations as per scenarios described under Type V.

Note: The change in manufacturing site for this condition will not be considered if the change is made without acceptable justification or submitted too frequently.

A change of manufacturing site under a **crisis situation** may be considered for a change between contract manufacturers for local natural and health supplement products.

Validity of registration for a product approved for change of manufacturing site remains unchanged.

2. TYPES OF COS

No.	Types of COS		Description
1.	**Type I**	Change of manufacturing site within Malaysia	Change of location of the site of manufacture within Malaysia only. This change may be due to upgrading of facilities, and/ or expansion of manufacturing activities or moving to a newly constructed plant, or appointment of a contract manufacturer for pharmaceutical products.
2.	**Type II**	Change of manufacturing site from foreign country to Malaysia	Change of location of the site of manufacture from outside of Malaysia to a location in Malaysia. This change may be due to the ability of the local counterpart to manufacture the product, or appointment of a contract manufacturer for pharmaceutical products.
3.	**Type III**	Change of manufacturing site located outside Malaysia	Change of location of the site of manufacture to manufacturing facilities located outside Malaysia. a) From a manufacturer to its own/subsidiary manufacturing premise ➢ This may be due to a merger or rationalization of manufacturing sites in line with manufacturing strategies. ➢ Applicable for all product categories b) From a manufacturer (its own/ subsidiary/ contract) to a contract manufacturing premise* c) From a local manufacturing site (in Malaysia) to manufacturing facilities located outside Malaysia (its own/subsidiary/contract)* *Applicable <u>only</u> for the following product categories: i. new drug products ii. biologics iii. generic products containing scheduled and non-scheduled poisons iv. veterinary products

No.	Types of COS		Description
4.	**Type IV**	Change of manufacturing site for sterile products	Change of location of the site of manufacture for sterile products: • within Malaysia • from outside Malaysia to a location in Malaysia • from Malaysia to manufacturing facilities located outside Malaysia • between sites located outside Malaysia a) From a manufacturer to its own/subsidiary manufacturing premise ➢ This may be due to a merger or rationalization of manufacturing sites in line with manufacturing strategies. b) From a manufacturer (its own/subsidiary/contract) to a contract manufacturing premise
5.	**Type V**	Change of manufacturing site in crisis situation	i) Change of location of the site of manufacture that is deemed necessary due to certain circumstances such as natural disasters, closure or suspension of premise (revocation of manufacturing license), bankruptcy and matters related to breach of product quality, safety and efficacy ONLY. ii) Prior to submission of Type V COS, approval letter issued by the secretariat of the Authority shall be obtained. iii) Application for Type V COS must be made within **six (6) months** from the date of the crisis. iv) Type V COS applications for natural products and health supplements are only applicable for local manufacturers.

3. MODE OF SUBMISSION

Applicant shall submit the application via the QUEST system.

4. SUPPORTING DOCUMENTS REQUIRED FOR COS APPLICATION

4.1 PHARMACEUTICAL PRODUCTS

Kindly refer to the *Malaysian Variation Guideline for Pharmaceutical Products (MVG)* where applicable.

4.2 BIOLOGICAL PRODUCTS

Kindly refer to the *Malaysian Variation Guideline for Biologics (MVGB)* where applicable.

4.3 ALL OTHER CATEGORIES OF PRODUCTS

For the list of documents to be submitted for each type of COS applications, kindly refer to the table below:

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
1.	Letter of authorization/ appointment from the product owner to authorise Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.	√	√	√	√	√
2.	Letter from the manufacturer/ product owner to clarify/ explain the need to change site of manufacture.	√	√	√	√	√
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry (check) specifications of the product as the same as already approved. *OR* If there are minor changes, to declare the 'minor changes' & justify the need for such changes.	√	√	√	√	√
4.	'Release' and 'end-of-shelf life' specifications from proposed site.	√	√	√	√	√

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
5.	Original copy of the Certificate of Free Sale (CFS) / Certificate of Pharmaceutical Product (CPP) and notarised Good Manufacturing Practice (GMP) from the source country of the new manufacturing site in the case of an imported product *OR* Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.	√	√	√	√	√
6.	Specification of the drug substance	√	√	√	√	√
7.	Product formula/ Batch Manufacturing Formula	√	√	√	√	√
8.	Original copy of Certificate of Analysis (CoA) from the new manufacturing site.	√	√	√	√	
9.	Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action).	√	√	√	√	
10.	"Accelerated" and on-going stability data as per ASEAN Guideline on Stability Study of Drug Product or Health Supplement/ Traditional Medicine and a letter of commitment to submit real time stability data.	√	√	√	√	
11.	Amended immediate label, outer label and package insert for the product from the proposed site.	√	√	√	√	√
12.	Process validation report as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration.	√	√	√	√	

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
13.	Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).	√	√	√	√	
14.	Letter of commitment to submit stability data, certificate of analysis and process validation report (where applicable) within 6 months of approval of site change.					√
15.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.	√	√		√	
16.	Comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer to circular:* *Bil. (31) dlm. BPFK/PPP/01/03* *OR* Report of bioavailability and bioequivalence studies for generic products. *OR* Comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. (*Please refer to ASEAN Guidelines and list of products requiring BA and BE study).*	√	√	√		

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
17.	Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer to circular:* *Bil. (31) dlm. BPFK/PPP/01/03* *OR* Letter of commitment to submit report of bioavailability and bioequivalence studies for generic products. *OR* Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. *(Please refer to ASEAN Guidelines and list of products requiring BA and BE study).*					√

<u>Note:</u>
No. 6, 9, 12, 13, 16 and 17 in the table above are <u>not applicable</u> for Natural Products and Health Supplements.

4.4 Supporting Documents Required for Type I COS Application (Natural Products)

No.	Documents to Be Submitted
1.	Letter of authorization/ appointment from the product owner to authorise Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.
2.	Letter of declaration stating the reason(s) for change of manufacturing site and clearly state the proposed and current name and address of manufacturer
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry specifications of the product as the same as already approved. *OR* If there are minor changes, to declare the 'minor changes' & justify the need for such changes.
4.	'Release' and 'end-of-shelf life' specifications from proposed site.
5.	Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.
6.	Product formula/ Batch Manufacturing Formula
7.	Amended immediate label, outer label and package insert for the product from the proposed site.
8.	Declaration and commitment that the manufacturer will carry out continuous quality monitoring on the post change products
9.	Letter of commitment to submit stability data and certificate of analysis after approval of site change.
10.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.

5. OTHER INFORMATION

a) Application for COS will be rejected if the applicant failed to submit required data within **six (6) months** from the first correspondence date;

b) All supporting documents are required to be submitted in accordance to the specified conditions for each type of COS.

c) If deemed necessary, NPRA reserves the right to request for additional supporting documents.

d) For further information, refer to:

i. *Bil. (59) BPFK/17/VF/9.2*
Prosedur Permohonan Pertukaran Tapak Pengilang Produk Berdaftar: Polisi Menolak Permohonan Pertukaran Tapak Pengilang Sekiranya 'Tiada Maklumbalas/ Maklumbalas Tidak Lengkap' Dikemukakan Oleh Pemohon Dalam Tempoh Enam (6) Bulan Dari Tarikh Permintaan (20 May 2009)

ii. *Bil. (22) dlm. BPFK/PPP/01/03*
Keperluan Kajian Bioekuivalens Bagi Produk "Generic Immediate Release Oral Solid Dosage Form" *yang Bertukar Tapak Pengilangan* (1 February 2009)

iii. *Bil. (31) dlm. BPFK/PPP/01/03*
Makluman Susulan Berkaitan Kajian Bioekuivalens Bagi Produk 'Generic Immediate Release Oral Solid Dosage Form' *yang Bertukar Tapak Pengilangan* (13 May 2009)

iv. *Bil. (39) dlm. BPFK/PPP/01/03*
Permohonan Pertukaran Tapak Pengilang Jenis V Iaitu Pada Situasi Krisis (16 July 2009)

v. *Bil. (10) dlm.BPFK/PPP/01/03 Jilid 1*
Directive No. 1, 2011*: Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik* "Immediate Release, Oral, Solid Dosage Form" *Yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian Bioekuivalens* (2 March 2011)

vi. *Bil. (7)dlm.BPFK/PPP/01/03 Jld. 3*
Kebenaran Pertukaran Tapak Pengilang Ke Pengilang Kontrak Tempatan (18 February 2014)

vii. *NPRA.600-1/9/12 (13)*
Pekeliling Berkenaan Peluasan Skop Permohonan Pertukaran Tapak Pengilang/Change of Manufacturing Site (COS) Type III dan Type IV (10 June 2022)