

**WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer**

**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)**

**Finished Product Manufacturer**

**Part 1: General information**

|                                                         |                                                                                                                                                                                           |
|---------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of Manufacturer                                    | May & Baker Nigeria Plc                                                                                                                                                                   |
| Unit number                                             | NA                                                                                                                                                                                        |
| Production Block                                        | NA                                                                                                                                                                                        |
| Physical address                                        | May & Baker Pharma Center,<br>1, May & Baker Avenue, Opposite Covenant University,<br>Off Idiroko Road,<br>Ota, Ogun State, Nigeria                                                       |
| Contact Person                                          | Nnamdi Okafor – MD/CEO<br>nnokafor@gmail.com                                                                                                                                              |
| Date of inspection                                      | 2 <sup>nd</sup> – 4 <sup>th</sup> October 2013 (WHO + NAFDAC)<br>5 <sup>th</sup> – 7 <sup>th</sup> May 2014 (WHO + NAFDAC)<br>12 <sup>th</sup> - 13 <sup>th</sup> September 2014 (NAFDAC) |
| Type of inspection                                      | WHO PQP Pre-submission Audit                                                                                                                                                              |
| Dosage forms(s) included in the inspection              | Oral Solid Dosage forms (Tablets) ONLY                                                                                                                                                    |
| WHO product categories covered by the inspection        | No submission yet but products under development with WHO-PQT (TA) assistance.                                                                                                            |
| Summary of the activities performed by the manufacturer | Manufacturing, Packaging, Quality Control and Batch release of Finished Pharmaceutical products (FPPs) in oral solid (tablets) and liquid dosage forms.                                   |

## **Part 2: Summary**

### **General information about the company and site**

According to the presentation made by the company, May & Baker was founded on September 4, 1944 as Nigeria's first pharmaceutical company. It was established as a subsidiary of its mother company, May & Baker plc based in Dagenham, in the United Kingdom. The company built its first factory at Ikeja, Lagos in 1976 where it began local manufacturing and packaging of pharmaceuticals. The company subsequently changed from May & Baker (West Africa) to May & Baker Nigeria Limited in that same year.

May & Baker Nigeria Limited became an independent publicly-listed company on November 10, 2006 when it became May & Baker Nigeria Plc.

The inspected site in this report is the company's new factory at Ota, Ogun State, Nigeria, which was commissioned in 2011. The company is currently in the latter phases of a project of product transfer to this new facility.

At Ota, Ogun State, the company performs manufacturing, packaging, quality control and batch release of Finished Pharmaceutical Products (FPPs), primarily oral solid forms (tablets and capsules), oral powders and granules and liquid dosage forms including suspensions. The products cover several therapeutic classes. The company has confirmed its interest and is preparing dossiers for a number of products within the EOI (expression of interest) for WHO PQ.

### **History of WHO and/or regulatory agency inspections**

The company had been audited at various times by NAFDAC, Standards Organization of Nigeria (SON) and the Pharmacists Council of Nigeria (PCN).

The company's Quality Management System is ISO 9001:2008 certified and receives regular inspections from its certifying body.

In addition, prior to these reported pre-submission audits by WHO PQ Inspectors, the company had received advisory visits by a team of WHO appointed consultants (with NAFDAC inspectors present as observers). These advisory visits focused on performing a gap analysis of general systems and particularly the production of oral solid dosage (Tablets) of formulations identified as having a high potential for future WHO Pre-Qualification. These visits were organised under the WHO PQ Technical Assistance Scheme. The most recent of these Technical Assistance visits was in July 2012. Prior to the first pre-submission audit by WHO Inspectors both the GMP

Advisors and NAFDAC had stated their opinion that the company had progressed sufficiently to enter the next phase of the joint project.

### ***Focus of the inspection***

The pre-submission inspections reported herein were WHO PQP Pre-submission Audits performed by members of the WHO Prequalification Team (WHO PQT) with NAFDAC Good Manufacturing Practice (GMP) inspectors present as observers and collaborators.

The overall pre-submission audit process involved two separate GMP audits, the first between 2<sup>nd</sup> and 4<sup>th</sup> October 2013 and second performed on 5<sup>th</sup> – 7<sup>th</sup> May 2014. Following review of the submitted CAPA (Corrective and Preventive Action) to these audits, a subsequent on/site verification of the implementation of the accepted CAPA plan was agreed with and performed by NAFDAC on 12<sup>th</sup> - 13<sup>th</sup> September, 2014. This WHOPIR is a summary of these collective activities.

The initial audit (2<sup>nd</sup> and 4<sup>th</sup> October 2013) was a risk based audit of a number of key GMP areas and systems, focused on those requirements of GMP that experience has found to be frequent sources deficiency. In particular these included the assessment of the robustness and effectiveness of key Quality Management System (QMS) sub-systems for handling deviations, incidents, root cause analysis and CAPA, the performance of effective quality monitoring and outcomes from periodic PQR (Product Quality Review), the selection, qualification, approval and control suppliers of critical raw materials and packaging materials and especially Active Pharmaceutical Ingredients (APIs), the handling of QC (Quality Control) samples and analytical data and particularly the reporting of OOS (Out of Specification) and OOT (Out of Trend) and laboratory error and their respective investigation. The design and monitoring of measures to control risks of cross contamination including heating and ventilation system (HVAC) design and the qualification and dust extraction and control, validation of process systems and cleaning was also a focus for this initial audit alongside a general facility audit of premises, equipment and manufacturing systems.

The second audit visit focused on the verification of site implementation of CAPAs to the observations of the initial audit and the review of procedures and systems related to those parts of WHO GMP that were not fully covered in the initial audit. The later included critical review of the extent to which the company had investigated the cited observations and particularly their root cause analysis of observations and the robustness of CAPA implemented or in process together with the mechanisms by which the effectiveness of the company CAPA would be assessed. The further review

included but was not limited to documentation and training systems, the purified water system, maintenance and calibration, and materials management systems.

Overall the two audits covered all key sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Following review by WHO Inspectors of the CAPA of the second audit, an inspection was performed by NAFDAC inspectors. This subsequent inspection focused on verification of the depth of implementation of the accepted CAPA, and allowed for a deeper review than that of documentation alone.

## **Inspected Areas**

### **The WHO on-site inspection on 5th – 7th May 2014 (WHO + NAFDAC) including the CAPA from the inspection of 2<sup>nd</sup> – 4<sup>th</sup> October, 2013**

The company had received the initial Pre-inspection audit for the potential WHO Pre-Qualification of an EOI product in Tablet form between 2<sup>nd</sup> and 4<sup>th</sup> October 2013 by a WHO expert inspector together with NAFDAC inspectors present as observers. The company had provided CAPA to these observations and following desk review and following subsequent follow up by NAFDAC to confirm whether substantial progress with remediation had been achieved, a further onsite audit was performed on 5th – 7<sup>th</sup> May 2014.

#### **Day I: 5<sup>th</sup> May 2014**

On arrival, an opening meeting was held with key personnel with brief introduction of the company representatives and the audit team.

The WHO inspector advised that the audit would involve a review and verification of the CAPA put in place by the company to address the observations made during the October 2013 visit for suitability and adequacy. He stated that the review would focus on the extent to which true root cause underlying the specific observations had been ascertained and corrected. He also emphasised the importance of continual improvement and stated he would assess whether the company had not just dealt with the specific observation but whether the company had improved their operations by attempting other areas where similar or related issues might be present but that were not specifically identified during the audit.

The company's Executive Director, Pharma Plant Operations provided a presentation on the facility which included a number of major changes that had occurred in the facility since the last audit:

- The company acknowledged that it operates in a region where sustainable and reliable uninterrupted commercial and government supplied power is a major problem, with obvious potential critical GMP concerns if not adequately mitigated. In a bid to forestall the challenge of power outages which could negatively affect the plant operations, the company had recently engaged a Third party Contractor for the provision of 1500KVA alternative power, contracted for 33MW power from the national grid for distribution in the plant. It had also procured a new 1250KVA generator with a back-up supply of diesel and provided a 60KVA Uninterruptable Power Supply (UPS) for critical instruments and equipment.
- Despite the fact that the facility was commissioned in 2011, and therefore less than three years old, during the previous visit a number of observations were made concerning the floors laid in the new buildings. It appeared that the original selection or laying of the floor by the contractors was significantly deficient leading to early deterioration of surfaces in various parts of the facility. The Inspector commented that floors are a common problem and emphasized that it is critical that these are well specified and laid by competent organisations fully conversant with both local conditions and the chosen flooring systems, if a good working finish and life are to be achieved.

The company had carried out re-surfacing of sections of the floors of the core areas in the plant using proprietary Ucrete Industrial Flooring which is stated by the supplier to have exceptional resistance to aggressive chemicals, heavy impact and thermal shock. The inspector was able to see test areas as well as zones where the floor had been re-laid. Finishes were very much improved.

- Company had also embarked upon a renovation of the chillers.
- The company had purchased a system for monitoring its production zone differential pressures from an overseas instrument company. These local monitoring devices were networked to a centralised logging and monitoring system. At the time of the previous inspection many of the devices supplied had failed rendering the centralised system of monitoring unreliable and the company was experiencing difficulty with replacements. In order to overcome the challenge posed by these malfunctioning centralized digital monitoring gauges for the control of the HVAC system, company had installed

decentralized analogue Magnehelic gauges and Thermo-Hygrometers for proper monitoring of environmental conditions of core process areas.

- During the initial visit in October 2013, there were a number of areas where the new facility was receiving significant damage due to poor working practices and behaviours. In certain areas there had appeared to be an acceptance of inadequate maintenance and design. During discussion at the time, the Inspector stated that this finding was most likely due to failures of management to set robust expectations, communicate these, and set systematic supervision in expectations of a good GMP standard. Previously there had been signs of local supervision tolerating issues (for example leaking pipe work or poorly installed services) and the results were demonstrably resulting necessity for major remedial maintenance when if the problems had been dealt with quickly and efficiently than the overall cost of remediation would have been less.

In response to these issues the Company had conducted intensive trainings of the Third Party Cleaners and company personnel on their attitudes, company processes and procedures; and proper equipment use. During May 2014 visit there was a demonstrable and significant improvement noted by the inspector suggesting that the actions taken had started to set a better culture of intolerance to the matters seen earlier. The inspector strongly encouraged continued sustained action in this area to try to ensure that the hard won gains were sustained and further improved, pointing out that to make such cultural change would require sustained managerial attention over a long period before the expectations were fully embedded into company culture in a sustainable manner. The company was however able to demonstrate that it well understood the challenges of maintaining the improvements and appeared strongly committed to this goal. Whilst some maintenance and installation standard issues were noted during the follow up visit, these were generally minor in nature.

- In the context of the above it was also noted that the Company had also conducted a full in depth review of its processes as regards to facility maintenance.

The company then presented the corporate CAPA plan for the previous observations and the comments made by the inspectors on a point by point basis. The majority of the remaining first day was given over to detailed CAPA review. Overall the CAPA had adequately dealt with previous specific symptomatic observations; however, the following general observations were made:

- Review of the CAPA from the last inspection showed that the specific observations were dealt with but frequently the root causes of the observations previously made were either not fully considered or not properly reported and documented in the CAPA plan.
- Since the first audit, the company had embarked upon the rapid transfer of products from their old plant to the new facility. Although there was a transfer team the project plans and deliverables were not well documented within a structured Quality Plan for the projects. The transfers for example had also proceeded without following a formal change control procedure/change management project plan within the QMS. In particular, there was neither formal QA reviewed project plan nor a comprehensive task list for both the general and specific points that needed to be addressed. Also, no formally documented risk assessment/impact assessment of the changes to be made was conducted before embarking on the product transfers. Project decision making rationale was also not well documented on a detailed level, with project minutes largely just documenting the problems encountered and the decisions made without there being adequate discussion.

The cleaning validation matrix had not been reviewed or updated with the introduction of each new product into the plant as should have been the case. These project organisational failures of product and knowledge transfer of cleaning protocols from the old facility had unfortunately resulted in an avoidable incident of contamination of one syrup product with residues of another due to the incomplete cleaning. The problem was identified during routine controls and had led to prompt rejection and therefore no patient risk. Following this issue, the company had implemented a new procedure specifically for the management of the introduction of new products into the plant, however this this procedure had not been fully incorporated into the QMS change management procedure. The fact that GMP Change Management and project management were essentially the same process was discussed.

- The company had a much improved Incident Reporting system in place as part of its QMS. At the initial inspection it was noted that further improvement was necessary as the Incident reporting logs did not provide adequate information to enable the linking of the incident to the corporate CAPA Management system as the actions taken were not comprehensively included in the remarks column of the logs. At that time it had been noted that some pending issues had in fact been signed off as being “okay” in the remarks column of the logs, whereas in practice only the immediate “correction” had been completed at the time this log was signed. In some instances reviewed earlier the full CAPA had still to be completed. The new procedure is more complex than that

previously and this is an area that the company should monitor carefully on an ongoing basis.

- A new SOP for Data Integrity/Back-up of HPLC Files had been written following the initial inspection. This covered the basics necessary but should be enhanced over time as it was considered relatively limited in content and importantly failed to give enough detail about execution of the policy behind the SOP. Although the procedure described various levels of access at a high level, the procedure did not fully define the detail “rights” associated with the user types (manager and operator access) and did not require confirmation of the user configuration. Back-up details did not adequately define all the file types to be backed up and how to verify that the back-up was sound and recoverable. It also appeared that there had been no full testing of back-up recovery. The SOP correctly stated that audit trail files were of similar importance to the data bins that were being backed up but the SOP did not fully describe in detail what parts of the audit trail needed to be checked and again the specific files to be retained were not fully defined to avoid possible inconsistency of process.

## **Day II: 6<sup>th</sup> May 2014**

After a brief re-cap of the observations made from the first day of the audit, the audit plan continued with a review of key QMS procedures commencing with a review of the company’s Incident Management procedure, Product Quality Review documents and an audit of the manufacturing and control of the prospective Pre-qualification product and similar products.

The following issues were observed:

### **Control of Starting Materials**

The approved vendor list was incomplete as the existing document lists the assessments of ARV and Anti-malarial APIs of interest to WHO PQT only. There was no listing for domestically circulated product requirements. It was stressed by the inspector that it was important that single ways of working were implemented and that there were significant risks in trying to run two systems for different markets. The supplier of Paracetamol (which is the company’s biggest product in terms of volume) was not included in this approved supplier list. It was found that there was in practice a second list being used by the procurement department which was not a QA controlled document. It was explained that this list was more comprehensive but included a number of companies (both manufacturers and brokers) where only a more limited assessment had been completed.

The company explained that it had three categories of API suppliers i.e. Manufacturers, Brokers and Suppliers with antecedents of satisfactory supplies. The company could show that it conducts different types of assessments for these suppliers including review of satisfactory inspection reports by SRAs, evaluation of Vendor Qualification forms and questionnaires; and audit of Nigerian brokers but this activity related primarily to the old plant. The company did not have any comprehensive document to show this existing final categorization/status of vendors and the level of assessments conducted, but was able to show evidence of individual assessments performed.

The company was able to share that it had a 2 year work plan to bring all materials into the newer more comprehensive system in the new factory and it was fully understood that it was a WHO GMP expectation that there should be a single vendor list approved by QA. However, how the mechanisms currently in place or in SOPs as to how the transition is to be managed was not clearly part of the product transfer project plan discussed above.

In a separate issue, the company had experienced an issue with two deliveries of Maize starch which had failed laboratory analyses on the grounds of high mould and viable count at levels which were acceptable for Food grade Maize Starch but not pharmacopoeial grades. These batches were promptly rejected, however investigation indicated that although the purchase orders clearly stated Corn Starch BP there was no evidence from the delivery notes from the broker supplying the material that this was actually what had been supplied was in fact pharmacopeia grade. Furthermore the company was unable to clearly demonstrate that the required full specification had been clearly communicated to the supplier and that he had accepted this. This indicated that the Supplier Qualification process was either deficient or that the requirements had not been fully explained to the supplier as it appeared from subsequent communications shown to the inspector following the rejections that the broker appeared to be unaware of the difference between Pharmaceutical grade and Food grade starch specifications.

### **Premises Design and Maintenance**

As indicated above this was generally much improved over what was seen at the initial audit. Several minor points were noted during this inspection:

- A clear liquid was observed to be dripping into the visitor change room from the ceiling close to the split A/C unit. This was immediately rectified however the actual cause of the problem was unknown and needed further investigation.

- Following trials, the company had commenced major renovation of the floors in the core processing areas of the facility but the project had a number of outstanding areas to be completed. A defined plan was provided and provided this was met to time this was considered acceptable. It was noted that the finishing around the drains in the Granulation room 2 was poor with rough edges and had recesses. This presents potential stress and failure points and need further detailed consideration if regular corrective maintenance is to be minimised.
- The company was in the process of installing overhead supply of granules into certain compressing booths however the installation standards were poor as there were gaps between the steel plates and the ceiling and therefore the plates did not flush with the ceiling. The company needed to work with the design and installers to better define what acceptable standards of work are. Subsequently photographic evidence of improvement was provided and verified on the ground by NAFDAC as described elsewhere in this report.
- The interlocks in the Compressing Modules were not working at the time of the inspection indicating a deficiency in the access control of these specific process areas. This observation was not made in other process areas where the interlocks were functioning as intended. The company subsequently made the necessary corrections.

### **Contemporaneous Recording of activities**

During the filling of a syrup product batch on 6th May, there had been a breakdown on the Filling machine on packaging Line 3 and the operation was transferred to the adjacent line (Packaging Line 2). Although an incident form had been raised and the Incident Report number was recorded in the Deviations section of the BMR, there was no other record of the immediate actions in the BMR indicating there was a problem. At the time of the audit the product was already on the second line but the deviation form and “correction” information had not yet been signed off by plant QA. Information such as the exact time the line stopped, set up records for the new line, line clearance information, number of packaging materials transferred, IPQA notes on the stalled operation were not recorded in the BMR. The IPQA personnel had signed off the incident as being closed whereas the incident had not been investigated nor fully rectified. Also leftover labels of the product were found on Packaging Line 3 indicating packaging material reconciliation process had not been completed on the line change over.

### **Validation**

At the time of the initial visit, only two of the twenty-nine products proposed to be manufactured in the new plant were recorded in the VMP to be fully validated. At the

time of the second audit further work had been completed and there were a significant number of products that had been transferred to the new plant and for which various trials had been performed. These trials whilst appearing reported in development reports and generally reasonable with respect to technical content had not been performed against clearly defined protocols with specifications and acceptance criteria not fully defined in advance of commencement of the trials. The development management of the project appeared to be outside the formal QMS mechanisms in place.

In particular:

- The company's prospective plans for the release of the trial batches to market in advance of a full review and formal validation report were not precisely defined. However, some batches have been released for distribution.
- Not all products had formalised hold time limits for intermediates such as granules, cores and bulk dosage form supported by scientific evidence and this had not been considered during process validation.
- Although the suspension filling line had stirrers on both hold tanks and the machine header tank the possibility of sedimentation in the transfer lines during longer line stoppages had not been investigated or covered in validation.

## **Investigation Procedures and Risk Management**

The finding of cross contamination referred to above had been recorded as a major (rather than critical) risk. The rationale for this categorisation of major rather than critical was stated to be because it had been discoverable by testing. This appeared to be not in accordance with the classifications in the company's own relevant SOPs. Discussion concerning classification of risks did not differentiate between potential risk (for example if the contamination had not been noticed) and the actual risk which in this case was low as the product was identified and immediately rejected.

Several of the CAPA to the previous inspection were essentially symptomatic "Corrections" rather than a full CAPA. The action taken adequately addressed the specific issues identified but the company had not identified the true root cause in certain cases and had not sought out the possibility of similar observations to arise in other areas and implemented Preventive Action. This is an area that the company needs to continue to work on over time. It has an action plan that is acceptable and the robustness of investigations is a matter that will be monitored in future inspections and by NAFDAC.

Although the transferred processes were very similar to those at the company's old plant in Ikeja, Lagos, unfortunately no formal comparison, risk assessment or review of historical data from the old plant had been performed.

### **In-Process Material Management**

Segregation of In-process materials in the staging area adjoining the Granulating suite in Module 2 was weak. Dispensed materials for three batches of a Tablet product were kept on three pallets on day two of the inspection and segregation between two of the pallets was not ideal. The nature of the packaging and number of bags were in the opinion of the Inspector such that it could easily lead to mix-ups. Whilst it is recognised that all were labelled with content and batch and that checks are performed during mixing additions it was nonetheless considered that improvements should be made. The subsequent changes to layout and caging of materials adequately deals with this point.

### **Day III: 7<sup>th</sup> May 2014**

An overview of the observations made on the second day of the inspection was done and the plan for the day was discussed. This included the conclusion of the review of the Risk Management procedures, review of the Product Quality Review reports, Batch Manufacturing Records (BMR) for the trial batches of similar products, Analytical methods and the Stability program.

The following issues were observed from these reviews:

### **Documentation Practices**

- Analytical data from trial batches were stored in log books and records with short (5 year) disposal dates. Although this would be considered satisfactory for routine batches with 1 to 3 years shelf life it was pointed out that several of the batches were pivotal stability batches and this data could be required after the 5 year disposal period was exhausted. It was pointed out that data for any pivotal batches used in BE studies should also be archived for longer periods than routine commercialized batches.
- Log books were not always formatted in a manner that allowed full use and easy tracking of logged information. The company should review the formatting of logs as a holistic exercise to improve the ease of use, reduce the number of cross references and therefore their overall usefulness in investigations.

## **Batch Manufacturing Records (BMRs)**

Greater diligence is required in the completion and QA review of batch documentation with a number of weaknesses noted during the review of BMRs and appropriate corrections and corrective actions were subsequently taken or initiated to address these observations and the underlying weaknesses. In addition several observations were made by the inspectors that whilst being relatively minor in nature should none the less have been noted during batch review. The company has subsequently put additional resource to the QA activity that will assist in remedying this issue. The situation will be further monitored in future inspections.

## **Product Quality Reviews**

Procedures for PQRs were found to be deficient prior to correction in CAPA. Only PQRs for three products had been prepared for 2013 at the time of the May 2014 inspection and the drafts reviewed were yet to be completed. There was no formalised work plan to complete the whole programme and this is exacerbated by the current practice of reviewing on a calendar year basis which results in no work smoothing. In general these reports lacked a detailed critical discussion of the contained data with only relatively high level comments being made and several key areas of WHO GMP for PQRs had not been covered. Subsequently the company has improved resource available to manage the PQR programme and provided a suitable plan to bring the preparation of PQRs on track. The subsequent inspection by NAFDAC confirmed the plan was on schedule and that better review of data was being performed consistently with the omissions now covered in both reporting formats and in the subsequent reports reviewed.

## **Methods of Analysis**

The standard testing procedure for one FDC product was reviewed and it did not give sufficient information concerning how sample preparation was assured to be consistent. The procedure requires shaking of the powdered tablets in the mobile phase for 30minutes and enquiries revealed that the shaking is done by hand. It was noted that one of the API can be under recovered in sample preparation leading to potential OOS or OOT results being initially reported.

## **Stability Program**

The stability program administration was found to be deficient several areas with the original data for test results for various time points for the accelerated stability testing of batches of the product selected for review could not be traced. It was noted that there had been no logs for the complete reconciliation and custody of samples. In inspecting these elements of the QMS it was noted that there had been a change in the

personnel administering the stability program without a proper handover and change management. This appeared to have led to a mix-up and possible loss of samples and analysis results. This appeared to be a historical incident and it was noted that since the new responsible person had taken over there were no further incidents noted of this nature and the files for the recent studies were much better kept.

At the close of the inspection a list of draft observations was provided to the company so as to allow early commencement of developing its CAPA plan.

**Verification by NAFDAC on 12 – 13<sup>th</sup> September of the company CAPA and its implementation made in response to observations made in the May 2014 inspection by WHO and NAFDAC.**

**Day I 12<sup>th</sup> September 2014**

On arrival, an opening meeting was held with key personnel on the purpose and scope of the verification inspection. The NAFDAC inspector further explained that on behalf of the WHO Inspectors, all observations in the CAPA, already presented as closed, both major and minor would be verified. However, the audit would be conducted in much the same manner as a certifying inspection but with an opportunity for further gaps to be identified and discussed.

The company was informed that following previous inspections, if all observations were indeed found to be closed during the verification inspection then this would be reported to WHO and the company would be recommended to WHO as operating at an acceptable level of compliance with WHO GMP guidelines.

The inspection included a walk-through of the facility followed by an evaluation of the Quality system with emphasis on Deviations, Root Cause Analysis, Production area, documentation, training records etc.

The following comments and specific observations were made during the NAFDAC on site verification:

**Quality Management System Review Including Change Management and Validation.**

- As stated above, the earlier inspection had identified that the company had embarked upon a project for the transfer of products and materials from their old plant to the new facility without following a formal change control procedure/change management plan within the QMS. There had also being no formal QA reviewed project plan or task list for points that needed to be addressed while implementing the change.

Following CAPA implementation, a formal Change Management Plan and technology transfer procedure had been implemented and this was verified as being in place and of an adequately comprehensive scope. It was now consistently in use.

A retrospective review of the project work performed to date had been documented within the QMS and the procedure adopted for outstanding transfers. Furthermore, a project plan has also been drawn in line with company's work plan which stipulated amongst other things the schedule for transfer of the remaining products. A Project plan with detailed task list had been initiated and it was verified that this had been formally reviewed by Quality Assurance-Head to cover all aspect of the transfer. All relevant departments have been trained on the new Transfer of Technology (TOT) SOP. In addition, Risk assessment is now been done in accordance with transfer of technology (TOT) SOP for products awaiting transfer to the new plant.

Review of Historical Data was seen to be now carried out to enhance robustness of the process and personnel knowledge in the new site with respect to product being transferred.

Company has included contingencies e.g. logistics of importation and clearance of raw materials have been henceforth factored into future change management plans.

- It was previously observed that limited formalized and documented risk assessment/impact assessment of the changes to be made had been conducted before embarking on the product transfers. The newly updated SOP and reviewed protocols for TOT now in place showed that risks associated with processes, product, personnel and equipment have now been fully considered before embarking on transfer. A report of the risk assessment conducted before product transfer was seen in the finalized TOT reports for recently transferred products. Relevant risk assessment tools were utilized. A project/ Change management plan for the introduction of further products into the plant which at the time of the previous inspections had not been considered during transfer has been made operational for the subsequent transfers and detail incorporated accordingly in the change management procedure.
- Previously trial runs of some processes were performed without adequately defined protocols indicating specifications and acceptance criteria. The trial runs reviewed in this visit were seen to be now guided by an appropriately approved Protocol detailing such areas as Scope, Objective, Execution Team & Responsibilities, Process Flow Chart, Deviations, Justification and Acceptance Criteria in the Validation Master Plan (VMP); documentation that

now properly defined trials, demonstration batches and commercial batches respectively.

- Previously, the company had released some products for distribution in advance of final documentation and reporting of a full review and the formal validation report being issued. Following CAPA it was verified that the company validation master plan now accommodated all validation program sign offs at specific times and dependencies on the transfer plan. Furthermore, all the company's products have now been captured in the validation master plan.
- The importance of formalised hold time limits for intermediates such as granules, cores and bulk dosage form supported by scientific evidence was not considered during previous process validations. Reports of completed hold time studies for bulk granules of some products were reviewed during this verification inspection visit while studies for other products were on-going against satisfactory protocols. There was also set plans for proper risk communication before embarking on further commercial batches.
- The possibility of sedimentation in the transfer lines during longer filling line stoppages had previously not being fully investigated or covered in process validation. The time of the verification visit a full sedimentation study for all suspensions produced at the plant had been concluded and the report was reviewed. The study monitored specific process parameters and Company had trained all relevant staff on the outcome of the study and process validation.
- In completing its CAPA to the last inspection it was considered that in some instances the Company had addressed specific observations without fully considering the root causes of the observations and where investigations had been conducted these were not adequately reported in the CAPA documentation Retraining on Root Cause Analysis/ Use of Investigational tools had been conducted. The company has now recognised that additional emphasis needs to be consistently placed on these factors if the improvements made by the company shall be sustained to ensure robust CAPA.
- The procedure for storage of analytical data of validation batches had been noted as inadequate as original electronic data was not fully retained and only the print out of data were stored in analysts' notebooks which had a short disposal period. Company however has now implemented an electronic back-up system for analytical data on an I.P. server.
- The previous SOP for Data Integrity/Back-up of HPLC files was limited in content and failed to give enough detail about execution of the policy behind the SOP. The execution of the HPLC data integrity policy had been reviewed to specify the identities, access levels and also responsibilities of users to ensure data security better defined. Implementation of these access levels was demonstrated.

## **Supplier Qualification process**

- It was observed during the previous inspection that those suppliers did not appear to fully understand the company's material requirements. All prospective and existing vendors supplying starting materials have now been forwarded a copy of the relevant materials specifications. During future vendor qualification the process now clearly requires a copy of Specification for Required Material to be attached whenever an official purchase order is made. Formal communication within the company to enforce compliance to the practice of adding material specification to official purchase order has been made.
- During the previous audits it had been found that there were multiple incomplete vendor lists and company did not have a comprehensive SOP and records to show the categorization/status of vendors and the level of assessments conducted. In response to this observation the company had reported that there was now a consolidated approved vendor list, controlled by QA. Categorization/status of vendors and assessments was verified as having been conducted and evidenced in the approved vendor list, taking into consideration track record of suppliers.

## **Observations made in previous visits concerning maintenance and construction standards.**

- The processing area drains were previously found to be deficient in sanitary and finishing had now been rectified and verified to be satisfactory during the site tour.
- During the previous inspection the installation standards used for the overhead supply of granules into certain of the compressing booths was found to have been poor predisposing the product to potential contamination from the interstitial area through ill-fitting coverings.  
Overhead supply of granules has now been made to flush properly with the panel to eliminate the possibility of contamination to products. As part of the preventive measures, facility-related jobs are now required to be subjected to formal design review and approval before implementation.
- Previously several of the interlocks leading to the Compressing Modules were not functional at the time of the initial inspection indicating a deficiency in the access control of these process areas. Routine preventive/ maintenance of electronic boards controlling the interlocks have been put in place at appropriate intervals. Training of personnel on appropriate use has also been carried out. Annexure for maintenance to give flexibility. Where routine

checks capture the need for immediate attention, maintenance there is now a formalized review process to assure that the work shall be done promptly.

### **Quality Management System (Incident reporting, investigations and CAPA)**

- During the previous inspection it had been observed that in some instances, Incident Reporting during processing was inadequate as reports were not detailed enough to give confidence that actions taken to resolve the incident ensured that product quality was not compromised. Incident reporting has been made more robust by giving greater details and post implementation review of executed CAPA. Continuing retraining on Incidence Reporting, using appropriate methods, has been carried out and additionally there is now greater emphasis on these aspects as a continuous process, with enhanced identifying key areas such as Investigation and Root cause analysis. The company has recognised that this is an area that it will need to keep revisiting to create a sustained improved process. In this respect a new post of Compliance Officer handling CAPA has been appointed to ensure that Incidences are adequately linked to company's corporate CAPA for visibility and prompt closures. Product BMRs had been reviewed and updated to include a section for a brief description of any incident/deviation during processing to ensure proper investigation and closure of same during batch review. Proper coordination and implementation is enhanced by the acquisition of additional reporting and tracking software for incidences, Audit observations, Self-inspection. CAPAs are in future to be tracked electronically to aid visibility, tracking and adequate evaluation. This process has also been enhanced by a revised training schedule for staff.
- During previous inspections, it was noticed that segregation of dispensed materials in the staging area was inadequate; the possibility for the occurrence of mix-ups had not been minimized adequately. Subsequently, revised storage practices have been implemented and additionally floor markings were made in the staging areas to ensure improved and clearer segregation of dispensed material. Training of responsible personnel had been conducted. The compliance monitoring had also been enhanced to enforce strict adherence to company's improved and established staging patterns.

- **Day II: 13<sup>th</sup> September 2014**

The plan for the day was discussed and included a review of the Batch Manufacturing Records (BMR) for the product of interest and Product Quality Review (PQR)

### **BMR and related Records**

Review of the BMR and related records revealed the following:

- The batch review procedure was previously considered deficient as incomplete and insufficiently documented attention was not evident to certain relevant details which were considered important to product quality during the BMR review process in place at the time. An increased tier level of BMR review had been instituted by on-line monitoring of documentation by appropriate personnel.
- In the previous inspections it was noted that there were weaknesses in document management procedures when effecting changes to batch documents. Subsequently, Changes made were effected through a formal change control system and all changes reviewed were seen to be properly logged.
- Initial inspections showed that Batch manufacturing records did not make adequate provision for proper documentation of certain processing activities. Currently, provision of adequate spaces to capture all indicated production processes had been made in the reviewed BMRs.

### **Product Quality Review (PQR)**

- While the work plan for PQR completion was available at the previous inspection (and the information therein) was adequate, there was however no evidence of version control of the documented plan. The work plan has now been made as a controlled annexure to PQR SOP and change history updated accordingly.
- During earlier inspections it had been noted that not all the criteria included in WHO GMP were included in the PQR review format. In particular there was insufficient information about the APIs, stability tests and technical agreements with suppliers. The PQR format and SOP has now been updated to capture all these important information. PQRs also now contained increased detailed discussion of data, with subsequent improvement of its content. As well as structure

### **QC Laboratories**

- The standard testing procedure for a particular product did not give sufficient information concerning how sample preparation was assured to be consistent. Mechanical shaker has now been installed and qualified to assure consistency in extraction of the APIs during analysis of Tablets and other products requiring extraction. The machine has been qualified and suitable operational procedure developed.

## **2.1 QUALITY ASSURANCE**

The company had the necessary procedures for evaluation and monitoring of product performance and quality of the systems through annual product reviews, and management reviews. At the time of the initial inspections there were procedures in place for the key core systems including change control and deviations, complaints and recall, and the qualification of equipment and systems and validation of procedures and processes. At the time of the initial inspection, the quality system exhibited a number of weaknesses in some but not all of these systems and opportunities and the need for improvement were identified in a number of areas. This was especially the case in the robustness areas of handling deviations; change control and root cause analysis where improvement was necessary. These systems have now been, such that it can be considered that the quality systems are adequately implemented. There is need for continuous improvement of the system and the improvements to be fully bedded in and sustained improvement demonstrated especially in the areas of handling deviations, change control and root cause analysis.

## **2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

The facility was a spacious, well laid-out multi-product facility with good quality equipment. The system was designed to support the manufacture and control of the product of interest in compliance with good manufacturing practices however improvements in the monitoring of the proper functioning of the HVAC system to assure that adequate environmental controls in the core processing areas and effective facility maintenance will enhance compliance with good manufacturing practices.

Controls over risks of cross contamination were generally acceptable although improvement in staging practices for dispensed raw materials was identified and rectified need. .

## **2.3 SANITATION AND HYGIENE**

There were cleaning procedures in place for the premises and equipment and generally the manufacturing areas, warehouse, corridors and cloak room were clean and tidy. Specifically, the floor cleaning system had improved compared to the initial inspection.

## **2.4 QUALIFICATION AND VALIDATION**

The validation master plan was in place and from the working document it was observed that several procedures and processes had been validated while others were

at different stages in the validation process as products were being transferred from the old facility.

The organisation of technology and product transfer from the old facility was underway during the initial inspections and this had not formally been taken through the change control process. Similarly the project plans for the transfers were not initially formally agreed through the QMS. Despite this it was clear that the process of technology transfer was being managed but there was significant risk of loss of product knowhow on transfer due to the lack of more formal documentation than what was available.

The company have a number of suspension products and it was a concern that the risk of sedimentation during longer stoppages had not been adequately explored during the transfer into the new filling line and during validation. These shortfalls have been addressed adequately in the CAPA plan and further studies.

## **2.5 COMPLAINTS**

SOP for formal review of product quality complaints was in place and appeared satisfactory with no significant comments made

## **2.6 PRODUCT RECALLS**

Procedures for product recall have been put in place to include parameters for exported products. The procedure provides for indication of who will be responsible for the recall in the importing country .in order to liaise with the regulatory authorities.

## **2.7 SELF INSPECTION AND QUALITY AUDIT**

The company has a satisfactory self-audit program as audits are conducted and closed after the audit report but non-conformances and deviations were found at initial inspection to be documented and followed up using a number of different logs and forms. The company would benefit from the use of a more unified CAPA system and tracking system.

## **2.8 PERSONNEL**

The company personnel were generally knowledgeable and cooperative and it was noted that there was generally a good level of expertise in key personnel.

The organisation appeared to generally have adequate staff in production and engineering departments. Similarly there was adequate expertise in the QC area. In the area of QA it was considered that the BMR review and CAPA programme and investigations system should be better resourced especially as the system and investigations become more robust with more incidents now being captured. The agreed CAPA included improvements in this area.

## **2.9 TRAINING**

From the review of some of the personnel training records, it was observed that the records were now duly updated as schedules for trainings established. Training system is adequately robust, training records have now been updated and the SOP on training has been updated following the inspections.

## **2.10 PERSONAL HYGIENE**

A satisfactory level of personal hygiene of the personnel was observed as they wore clean apparel including head coverings where required, as appropriate to the duties performed.

## **2.11 PREMISES**

The premises were well laid-out and appropriately designed, constructed, maintained and cleaned to suit the operations carried out and facilitate sanitation. The HVAC system was suitably designed, installed and maintained.

## **2.12 EQUIPMENT**

The company had good quality equipment which were designed, located and maintained to suit the operations and permit effective cleaning and maintenance.

## **2.13 MATERIALS**

Receipt, storage and dispensing of materials have generally been improved and were satisfactory.

The company has established and operating a system of supplier qualification but in common with other Nigerian companies visited the sector has considerable challenges due to the involvement of a significant number of brokers in the supply chain. Most APIs are imported and those from quality assured sources attract significant premiums. Some supply chains back to the original manufacturers are quite long so continuity and sustainability are significant challenges.

## **2.14 DOCUMENTATION**

The company has a document issuance and authorization system in place with further improvements in documentation practises implemented following observations of the initial inspection. Also item codes are now consistently and comprehensively used in process documents and specifications. Electronic backup systems were now in place also. In common with the other Nigerian companies visited, the comprehensive use of unique item codes for materials was underutilised. Following the CAPA to the inspections these codes were now more consistently and comprehensively with a rolling programme of updates to extend their use to all process documents and specifications etc.

## **2.15 GOOD PRACTICES IN PRODUCTION**

Generally, production activities were carried out satisfactorily as they were performed in accordance with batch documentation and in line with GMP principles.

## **2.16 GOOD PRACTICES IN QUALITY CONTROL**

The Quality department carries out the requisite functions of the Quality Control Unit as regards sampling, testing, organization, documentation and release of materials and products.

There were initially some observations on data management on the HPLC and GC systems especially regarding data back-up. The HPLC systems were restricted only to analysts with log on passwords and activated audit trail, therefore every activity can be tracked to the operator.

## **Part 3: Conclusion**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the two WHO pre-submission inspections, including the observations listed in the Inspection Report, as well as the corrective actions taken and executed, and verified by NAFDAC, the facilities and operations for oral solid dosage forms at May & Baker Pharma Center, 1, May & Baker Avenue, off Idiroko Road, Ota, Ogun State, of *May & Baker(Nigeria) Plc* were considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, and verified on site by NAFDAC inspectors prior to the publication of this WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.