What is Lean?

- A **time-tested method** and set of tools to help us improve **“how”** we produce our **products** and **services**.
- Lean is also a mindset, where we ask each day **“How can we make our services better for customers?”**

Lean is about Simplifying our Work

- **Eliminate tasks** that do not **add value**
- Make things **easy** and **intuitive** for **customers** and **staff**
- **Automate** repetitive tasks
- **Leverage staff talent**

Why Lean?

- ❑ Reduce product and service **cost**
- ❑ Enhance **customer** satisfaction-⬇ complaints
- ❑ Increase **staff** engagement and morale
- ❑ Improve services **quality**
- ❑ Increase **accountability**
- ❑ **Increase predictability**
- ❑ Improve **speed** of service-eliminate waste
- ❑ Increase **consistency**
- ❑ Documented processes-**fast induction of new staff**

Lean helps us improve **quality**, **reduce costs**, **increase customer** and **employee satisfaction**, & capture knowledge

Lean Healthcare

Applying lean principles to healthcare processes to **improve patient outcomes**, **reduce wait times**, and **increase efficiency**

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

Microsoft Teams

MCAZ Feedback on the new system of processing applications for registration: Circular 26 of 2023

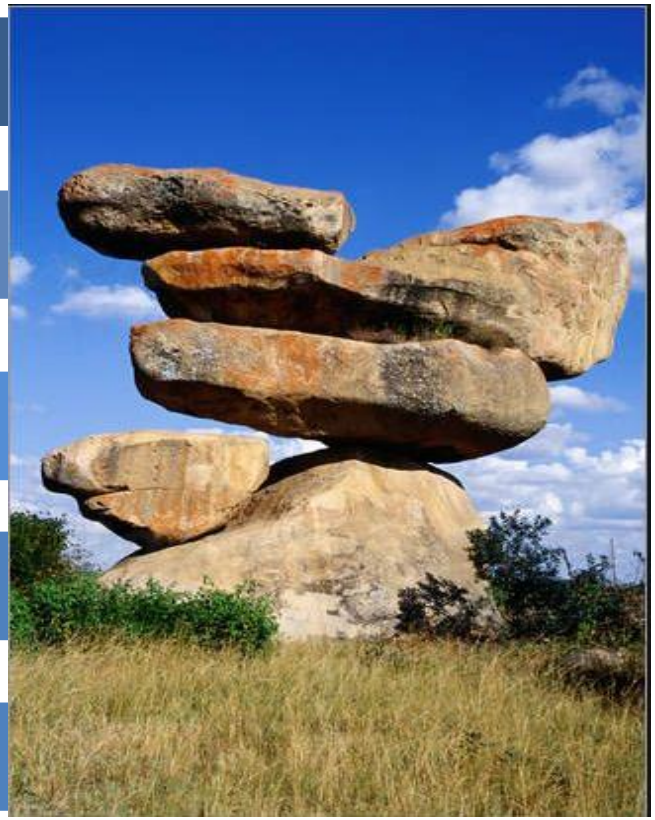
25th April 2024

Zivanai Makoni Dr.
Chief Regulatory Officer – Evaluations (EVR)
106 Baines Avenue
Harare
zmakoni@mcaz.co.zw

MCAZ

Agenda

- Background to MCAZ Registration Process
- Lean Healthcare: Circular 26 of 2023
- Lean Healthcare: Automation
- Challenges
- Way forward



MCAZ's Mandate

Protect and Promote Public Health & Animal Health

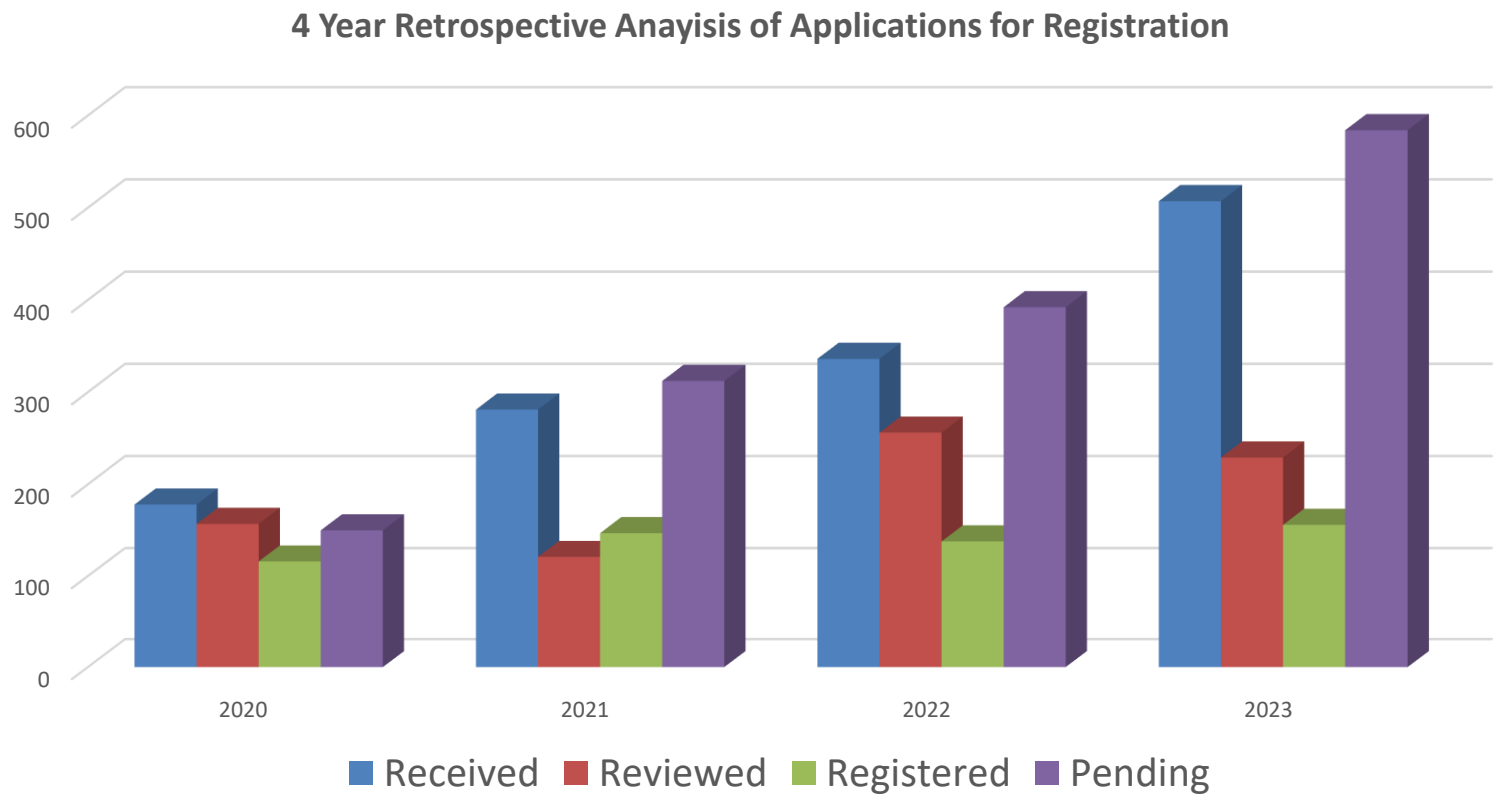
By assuring that medical products marketed in the country are SAFE, EFFECTIVE and of GOOD QUALITY

Lean Healthcare

- Human Allopathic Medicines Unit
- Veterinary Medicine Unit
- Complementary Medicines (Human & Veterinary) Unit
- **Staff Complement of 30 staff**

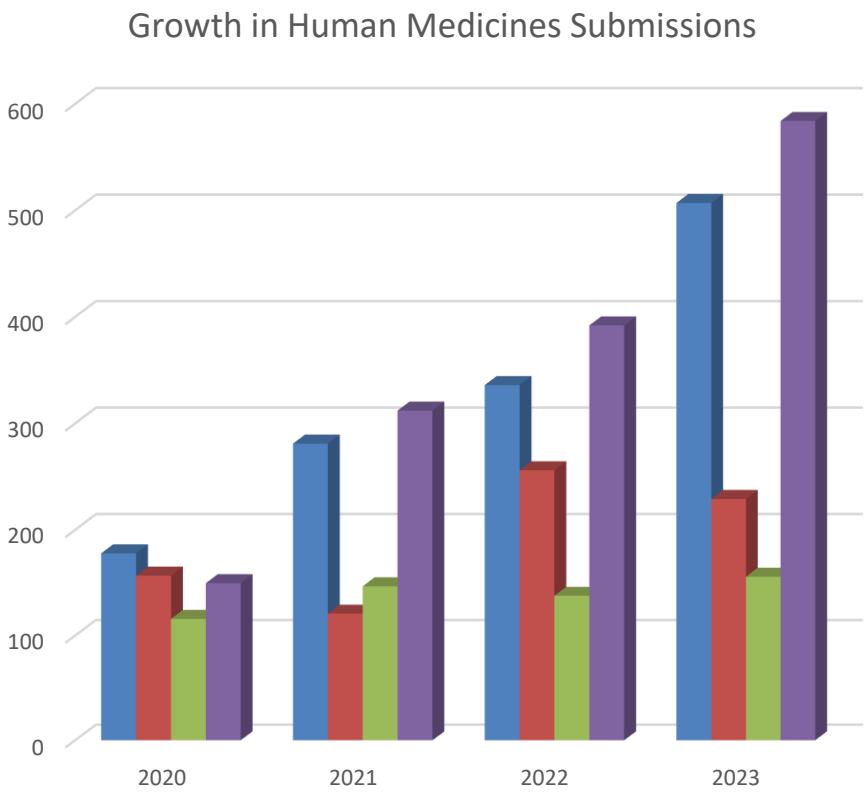
- 3 Managers
- 5 Admin staff
- 22 assessors
- 18 assessors currently manning all **three product lines**
- 4 experienced assessors left the Division (November 2023 to April 2024)

Background to MCAZ Registration Process



Background to MCAZ Registration Process

Human Medicines Unit



Human Capital

- ❑ Staff Complement has not changed since 2019
- ❑ Staff attrition is perennial

Workload

- ❑ Submissions of new applications for registration has tripled
- ❑ Backlog has tripled 2020 vs 2023
- ❑ WHO GBT brought about new workload [*Re-Registration/ Renewals & SMPCs*]

Mapping Exercise July – Sept 2023

- **Human Allopathic Medicines Unit (950 pending)**

  398: opened files *and* ***552: unopened files***

- **Veterinary Medicine Unit (40 pending)**

- **Complementary Medicines Unit (120 pending)**

Circular 26 of 2023

Observations

- ❑ Submission of substandard application for registration
- ❑ Multiple deadline requests
- ❑ Protracted Review Cycle: ≥ 6
- ❑ Increase in WIP: Reduction in Productivity
- ❑ General increase x3 in applications for registration
- ❑ Perennial Staff Attrition: Reduction in Talent
- ❑ Inefficient Tracking & Monitoring of Timelines

MCAZ Medicines Control Authority of Zimbabwe

REF: B/279/35/26/2023

CIRCULAR 26 of 2023

Date: 24/11/2023

To: ALL APPLICANTS, MANUFACTURERS AND PRINCIPALS

RE: PROCESSING OF APPLICATIONS FOR REGISTRATION OF MEDICINES

The Authority has, after consultation with stakeholders, significantly revised the processes for handling applications for registration of medicines. Stakeholders have complained over the years about the timelines for registration of medicines, which are considered to be too long. Further complaints have been around the communication of progress on the assessment of applications. After conducting an exercise in the third quarter of 2023 to map the status of all pending applications, the following reasons were noted as contributing to the inefficiencies and persistent backlog of applications in the system:

(1) Submission by Applicants of grossly deficient applications for registration.
(2) A significant number of Applicants requesting for multiple deadline extensions for submission of responses after receiving evaluation outcome letters.
(3) Protracted evaluation and response cycles between the Authority and Applicants at various stages of the evaluation and registration process, resulting in an increase in the volume of work-in-progress (WIP) over time.
(4) An increase in WIP resulting in increasing costs and reduction of productivity for the Authority without an accompanying increase in resources, leading to an ever increasing backlog of applications.
(5) A general increase in the volume of applications for registration received by the Authority.
(6) Staff attrition resulting in a decrease in the number of experienced assessors.
(7) Inefficient monitoring and tracking of timelines by the Authority.

The following are measures that the Authority will implement, starting in January 2024, in order to eliminate the inefficiencies emanating from a confluence of the above factors:

Screening

With effect from 1st January 2024, the Authority will perform high level screening of all applications for registration. This screening will be performed by the Authority's most experienced and most proficient assessors to ensure that applications that get accepted for evaluation are complete before they are cleared for the first assessment process.

Screening Timelines

For the screening process to be effective, the applicants must get rapid feedback from the Authority as soon as they submit their applications. The Authority is therefore committed to undertake screening for all applications within **ten (10) working days** of submission of an application. It is however noted that there are a number of pending applications in the backlog

2 YEARS

1 of 3

Medicines Control Authority of Zimbabwe (MCAZ)

Circular 26 of 2023

Solution

- ❑ High level Screening
- **-Pass:** Proceed to evaluate
- **-Fail:** NMT 120 respond
- ❑ Limit Review Cycles ≤ 2
- ❑ Regulatory Decision in NMT 9 months
- ❑ Previous Median Time to Registration **<u>24 months</u>**

that are yet to be assessed. To avoid further inefficiencies resulting from implementing multiple processes, these applications will also be screened prior to assessment, even though they have already been accepted and issued with Application numbers.

Applications failing screening

Applications that fail screening will be allocated with **Quarantine numbers**. A Quarantine number in essence means that the application is held in abeyance pending resolution by the Applicant of shortcomings noted during the screening process. **It is critical to note that there is no priority afforded to quarantined applications.**

Once an application is quarantined, the Authority will issue a letter to the applicant, intending to refuse to register the product, unless a complete application is submitted within 120 days. Failure by the Applicant to resubmit a complete application within the prescribed timelines will result in refusal to register the application and Applicants interested in pursuing such applications will be required to resubmit new applications accompanied by payment of the full application fee.

Upon resubmission of a complete dossier and payment of the statutory resubmission fees as stipulated in item 7(a)(ix), 7(b)(v) and 7(c)(iv) of the MCAZ Fee Schedule, applications will undergo a second round of screening. **Applications that fail the second round of screening will be refused registration without assessment**. It is also critical to note that in computation of the Authority´s timelines, quarantined products will be tracked separately from complete applications.

Applications passing screening

Application numbers will **ONLY** be allocated to complete applications that pass screening at first attempt or those that pass screening following resubmission of a complete dossier and payment of statutory resubmission fees as discussed above. **Only complete applications that are issued with application numbers will be admitted for assessment.**

Review cycles

With immediate effect, stakeholders are advised that the Authority will conduct a maximum of two (2) review cycles per product before reaching a **final regulatory decision** (*registration or refusal to register*). Applicants are advised to take all issues raised in the assessment report seriously to avoid exceeding the maximum number of review cycles. At the end of the 1st review cycle, applicants will be further advised to withdrawal their applications **voluntarily** if they cannot address the queries raised by the Authority. The Authority will reach a final regulatory decision at the end of the 2nd cycle.

Registration process regulatory phases

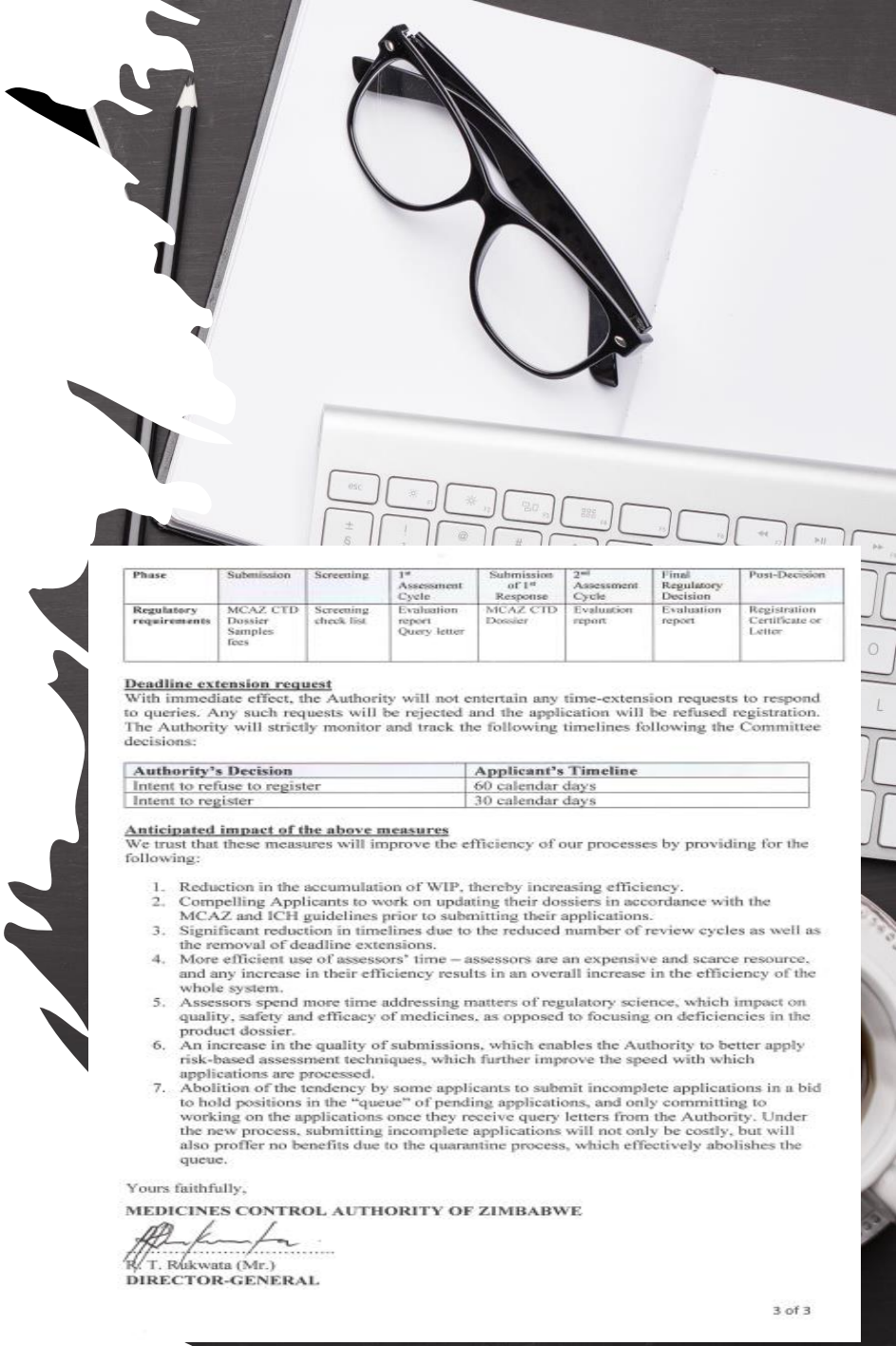
With immediate effect, the Authority will use a tracker (clock start-clock stop system) to efficiently monitor and track each application as a separate project as indicated below:

Phase	Submission	Screening	1st Assessment Cycle	Submission of 1st Response	2nd Assessment Cycle	Final Regulatory Decision	Post-Decision
Activity	Applicant submits Dossier	High level screening by MCAZ assessors	1st Assessment session by MCAZ	Applicant submits Response	2nd Assessment session by MCAZ	Final Committee decision	Administrative and Regulatory activities

Circular 26 of 2023

Anticipated Benefits

- ❑ Increase in efficiency in processing applications for registration
- ❑ Improvements in submissions: MCAZ/ICH Requirements
- ❑ Significant reduction in timelines for registration
- ❑ Efficient Talent Management
- ❑ Better Risk-Based Assessments on Quality submissions
- ❑ Abolishment of the tendency to hold queue by applicants with grossly deficient dossiers



Phase	Submission	Screening	1st Assessment Cycle	Submission of 1st Response	2nd Assessment Cycle	Final Regulatory Decision	Post-Decision
Regulatory requirements	MCAZ CTD Dossier Samples fees	Screening check list	Evaluation report Query letter	MCAZ CTD Dossier	Evaluation report	Evaluation report	Registration Certificate or Letter

Deadline extension request

With immediate effect, the Authority will not entertain any time-extension requests to respond to queries. Any such requests will be rejected and the application will be refused registration. The Authority will strictly monitor and track the following timelines following the Committee decisions:

Authority's Decision	Applicant's Timeline
Intent to refuse to register	60 calendar days
Intent to register	30 calendar days

Anticipated impact of the above measures

We trust that these measures will improve the efficiency of our processes by providing for the following:

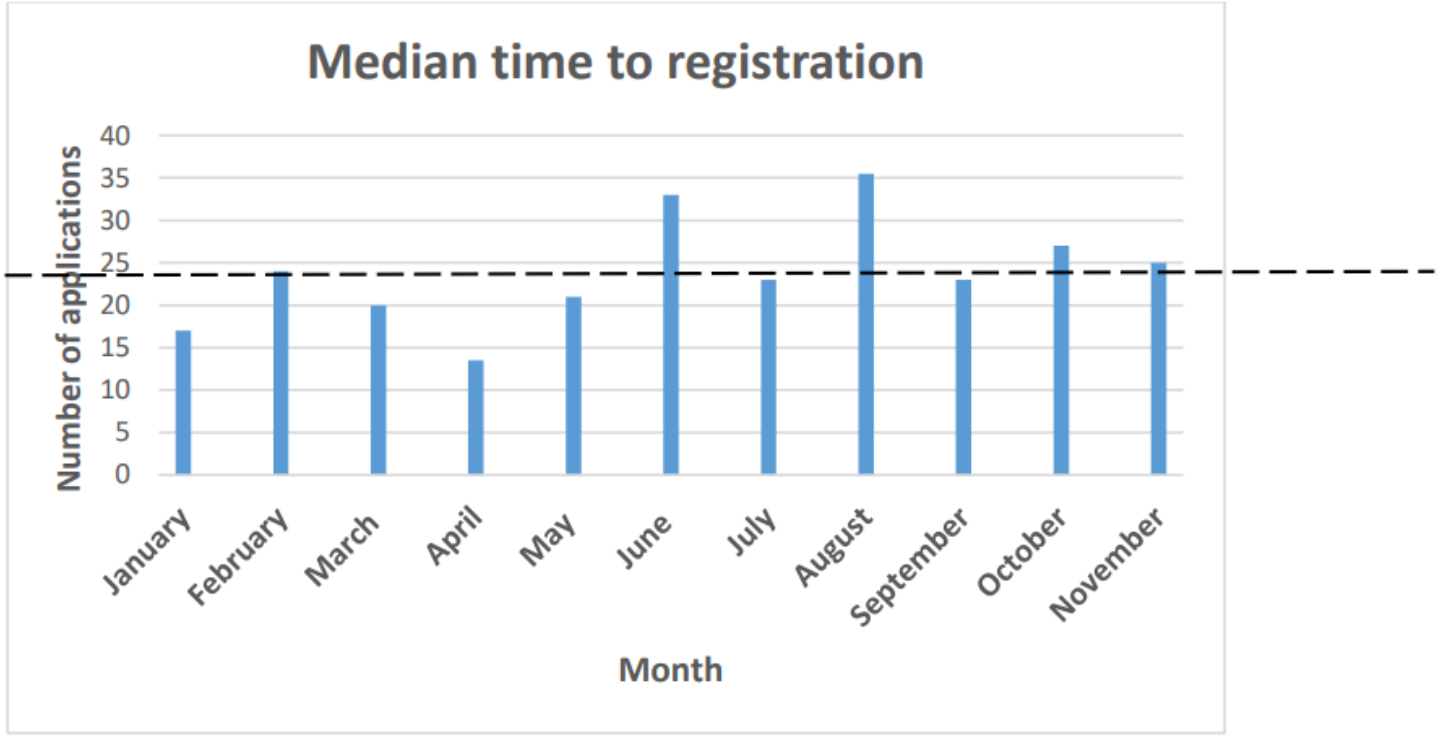
1. Reduction in the accumulation of WIP, thereby increasing efficiency.
2. Compelling Applicants to work on updating their dossiers in accordance with the MCAZ and ICH guidelines prior to submitting their applications.
3. Significant reduction in timelines due to the reduced number of review cycles as well as the removal of deadline extensions.
4. More efficient use of assessors' time – assessors are an expensive and scarce resource, and any increase in their efficiency results in an overall increase in the efficiency of the whole system.
5. Assessors spend more time addressing matters of regulatory science, which impact on quality, safety and efficacy of medicines, as opposed to focusing on deficiencies in the product dossier.
6. An increase in the quality of submissions, which enables the Authority to better apply risk-based assessment techniques, which further improve the speed with which applications are processed.
7. Abolition of the tendency by some applicants to submit incomplete applications in a bid to hold positions in the "queue" of pending applications, and only committing to working on the applications once they receive query letters from the Authority. Under the new process, submitting incomplete applications will not only be costly, but will also proffer no benefits due to the quarantine process, which effectively abolishes the queue.

Yours faithfully,

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

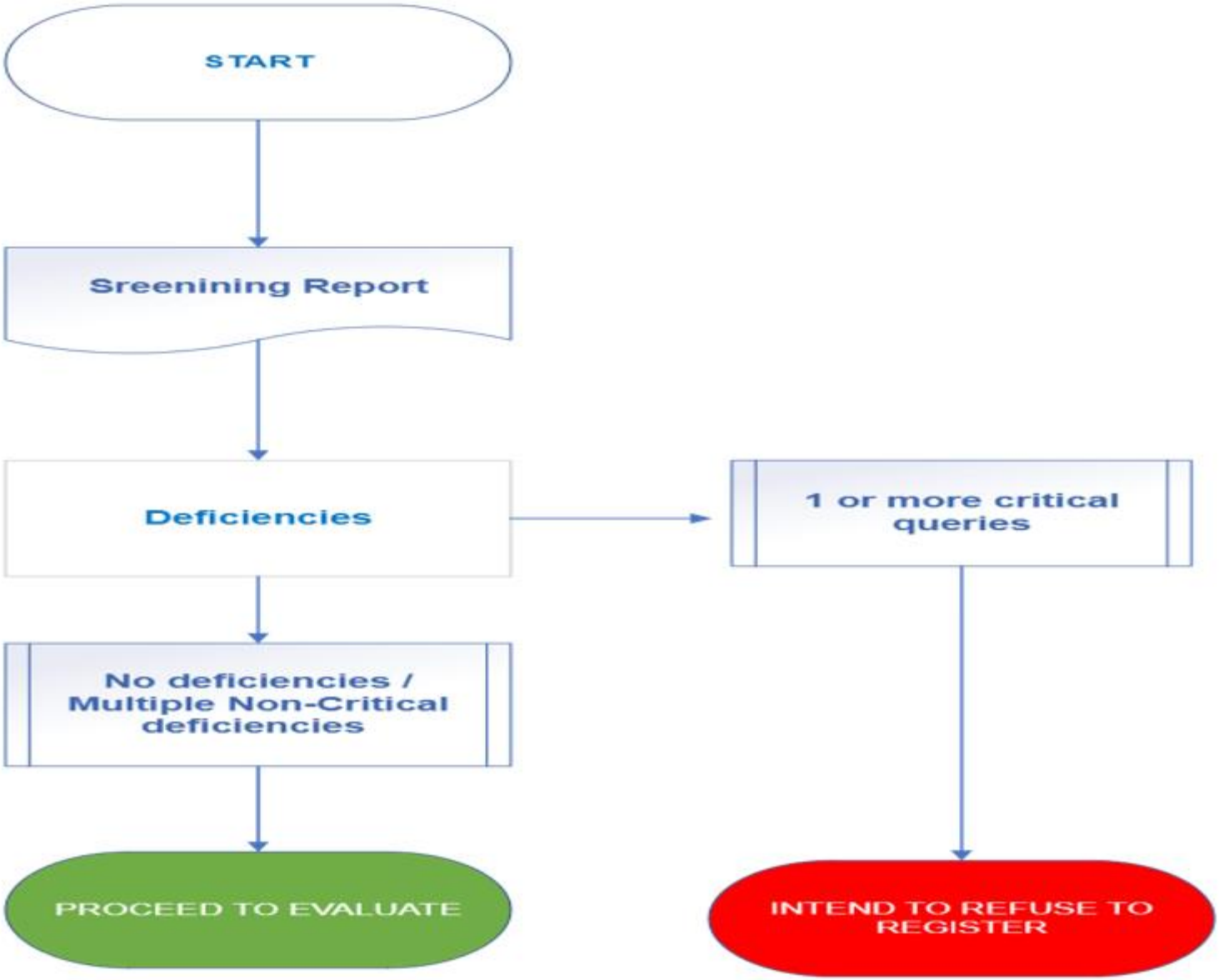
R. T. Rukwata (Mr.)
DIRECTOR-GENERAL

3 of 3



All 21 products that were registered in November came in via the normal route. The median tim to registration for the 21 products was 25 months. The range was 59 months as determined by maximum of 64 months and a minimum of 5 months. The monthly median time to registratio target is 24 months.

Screening Decision Matrix



Registration process regulatory phases

With immediate effect, the Authority will use a tracker (clock start-clock stop system) to efficiently monitor and track each application as a separate project as indicated below:

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Registration process regulatory phases

With immediate effect, the Authority will use a tracker (clock start-clock stop system) to efficiently monitor and track each application as a separate project as indicated below:

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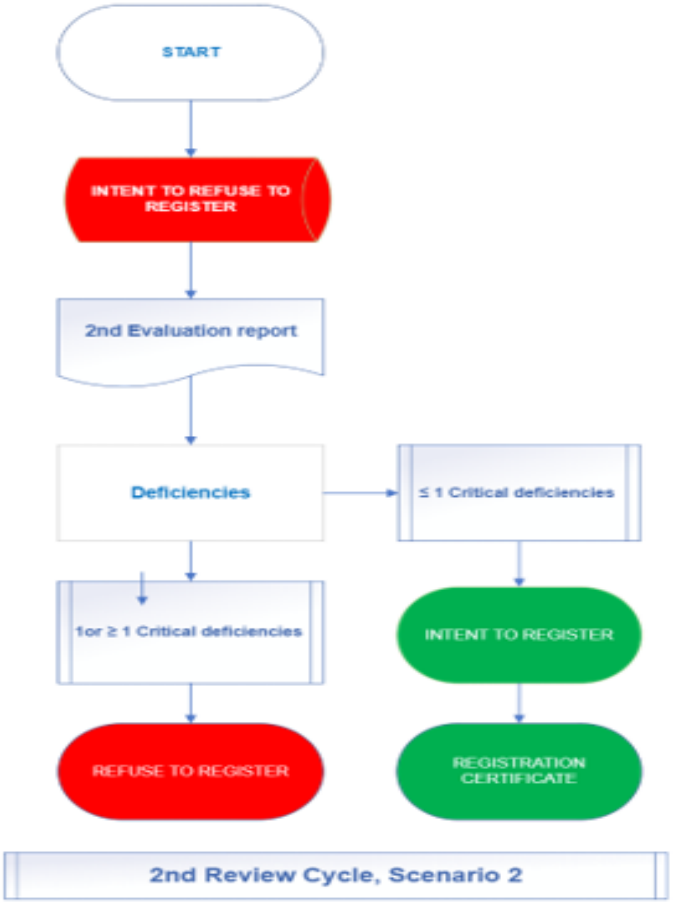


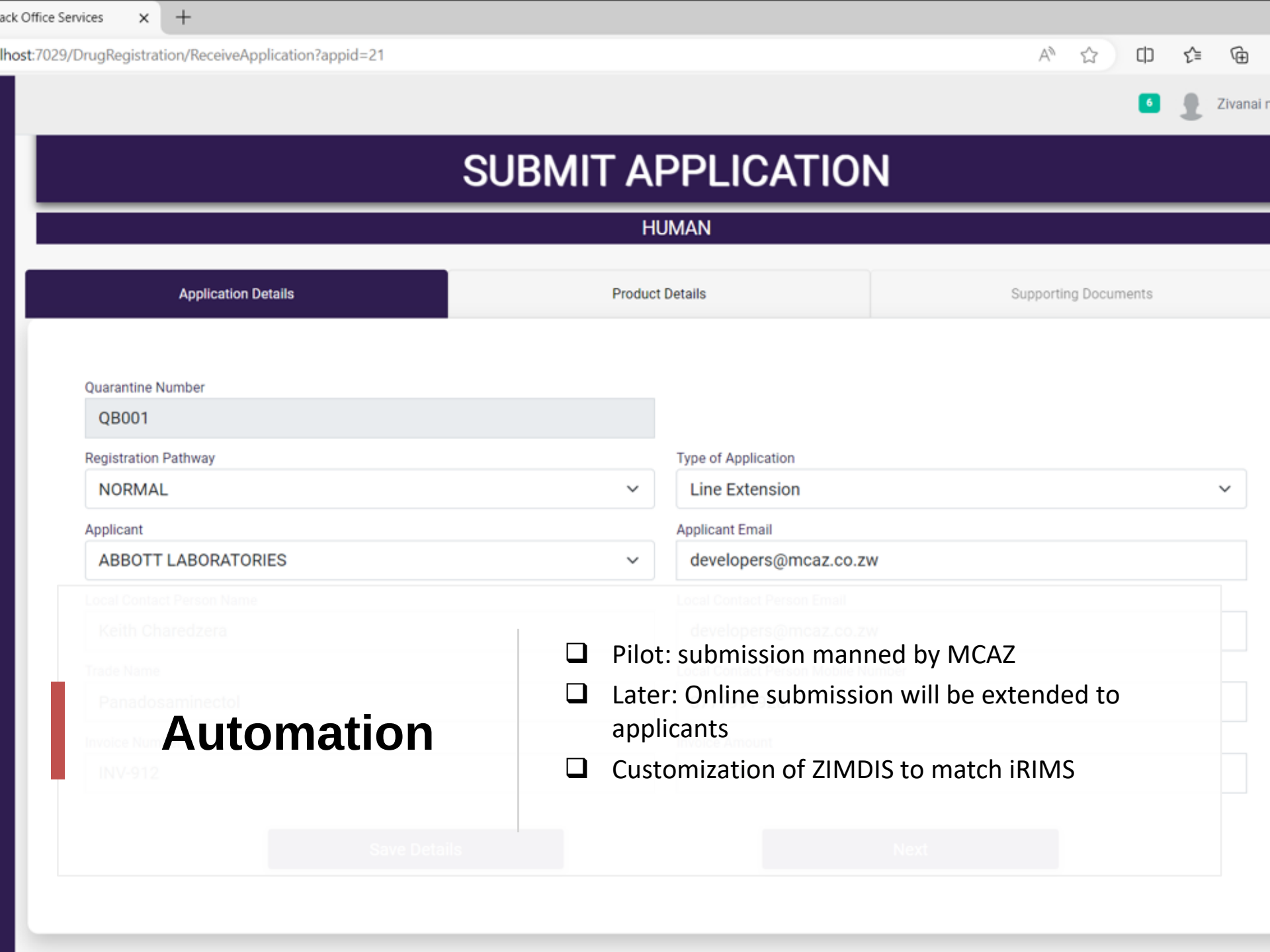
Automation

Innovation

- ❑ iRIMS: costly
- ❑ Development of the New ZIMDIS with online submission platform & tracking tool

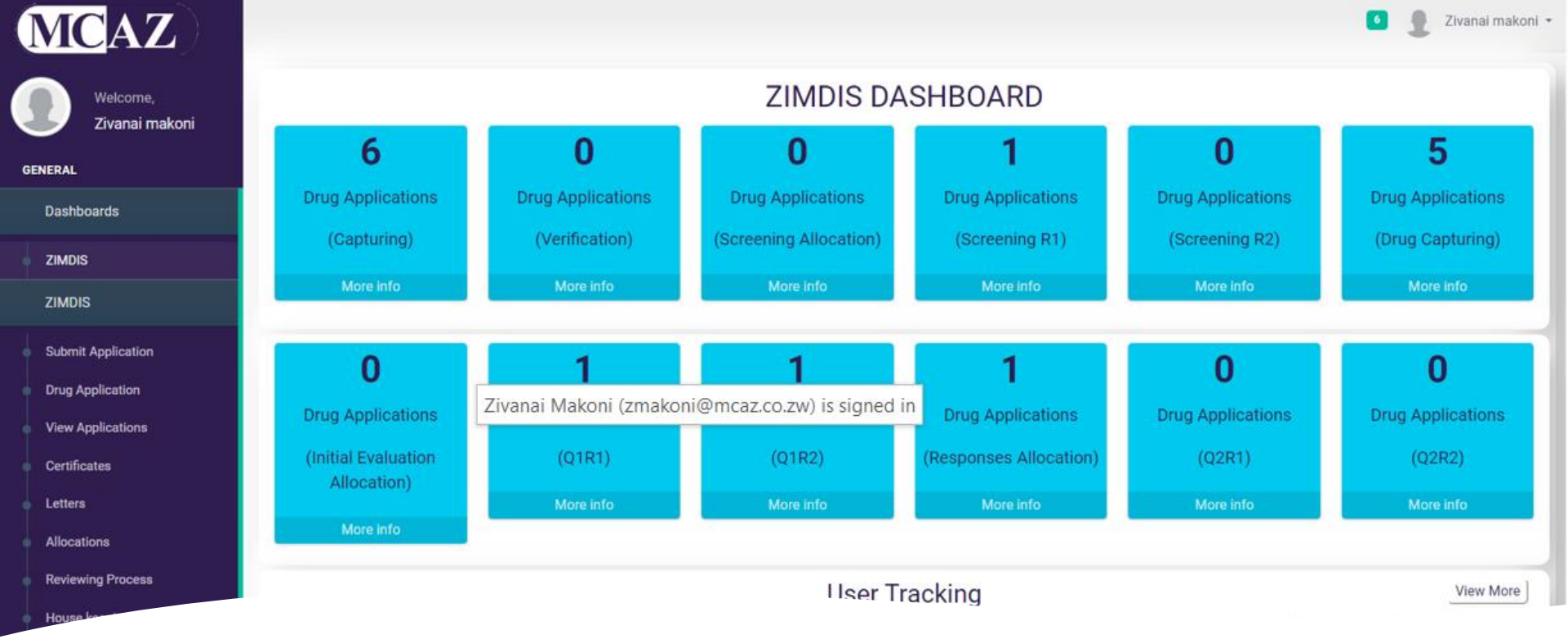
1. URS: December 2023
2. Prototype
3. UAT: April 2024

- ❑ Data migration: April 2024
- ❑ System Go-Live: April 2024



Automation

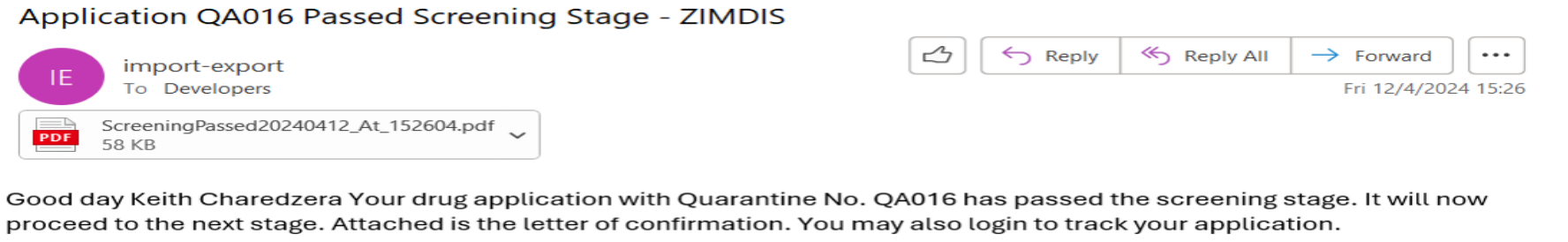
- ❑ Pilot: submission manned by MCAZ
- ❑ Later: Online submission will be extended to applicants
- ❑ Customization of ZIMDIS to match iRIMS

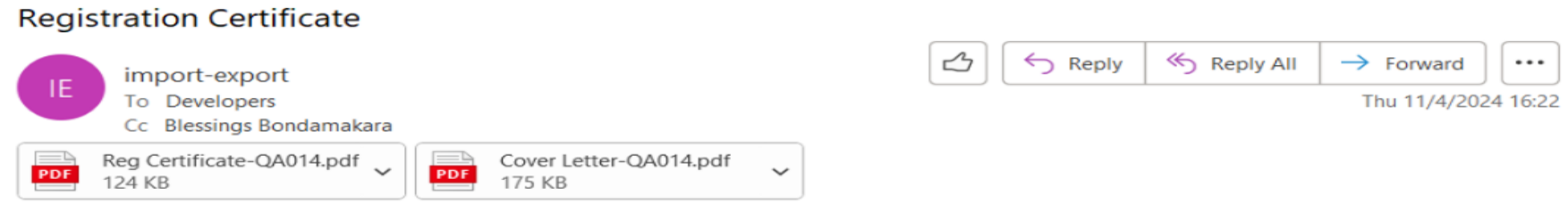


Automation

- End to End Processes under surveillance by Management Team
- All applications will be accounted for
- Efficient monitoring of key timelines

Automation





APPLICANTS RECEIVE NOTIFICATIONS ON KEY MILESTONES ON THEIR APPLICATIONS FOR REGISTRATION

SYSTEM GENERATES LETTERS & REGISTRATION REMOVING UNNECESSARY ADMINISTRATION ON ASSESSORS

EFFICIENT COMMUNICATION BETWEEN NRA AND INDUSTRY

COMMON SCREENING DEFICIENCIES

Human & Veterinary Dossiers

MODULE 1	
Cover letter	• Absence of signed and dated cover letter that includes the full details of the local representative, and this should have included the full name and email address of the responsible person.
MC8 form	• Incomplete, not signed, and dated MC8 form with incomplete details for example complete address of the principal and name of manufacturer.
Declaration by the applicant	• Absence of signed and dated declaration by the applicant attesting to the accuracy of the contents of the application.
Proof of compliance with current Good Manufacturing Practices (cGMP)	• Absence of valid cGMP certificates of API and FPP manufacturers
LABELLING AND PRODUCT INFORMATION	
Summary of product characteristics (SmPC)	• Absence of SmPC in MS Word version as was instructed
Labelling (primary and secondary packaging)	• Incorrect labels that not consistent with the requirements of Medicines And Allied Substance Control Regulations
Package insert and patient information leaflet	• Incorrect package inserts and patient information leaflet that not consistent with the requirements of Medicines And Allied Substance Control Regulations
Samples	• Absence of samples of the finished product packaged in the proposed container closure system.

COMMON SCREENING DEFICIENCIES

MODULE 3

3.2.S Drug substance - Active Pharmaceutical Ingredient (API) (S part)

Certificate of suitability of the European Pharmacopoeia (CEP).

- **Absence of CEP after claiming its use.**
- **CEP does not contain all the annexes (Manufacturer – Analytical procedures of any additional tests not specified in the European Monograph…)**
- **Box of authorization in the CEP is not filled or signed by the CEP holder.**
- **Absence of the acknowledgement commitment letter by the applicant to MCAZ in case of CEP withdrawal or updates.**
- **Absence of required sections of the S-Part (not covered by CEP), Example:**
  - **Absence of 3.2.S.6 (Container Closure System) (when CEP is not including the description of Container Closure System)**

3.2.S.2.2 Description of manufacturing process and process controls	• **Flow diagram of the synthetic process(es) is not describing all the manufacturing steps and critical process parameters.** • **Unacceptable starting materials (not as per ICH Q11)** **e.g. Azithromycin dihydrate -> Azithromycin trihydrate (as a single step)**
3.2.S.2.1 Manufacturer and address	Manufacturer and address
3.2.S.2.3 Control of raw materials	• Absence of control of all raw materials. • Details concerning API starting materials preparation is insufficient or missed.
	• Particle size distribution for low soluble API is not discussed • Hygroscopicity is not discussed • Polymorphism for low soluble API is not discussed

3.2 Manufacture

3.2.S.2.1 Manufacturers	• Addresses of manufacturing sites do not include blocks or units.

Human & Veterinary Dossiers

COMMON SCREENING DEFICIENCIES

3.2.S.2.2 Description of manufacturing process and process controls	• Flow diagram of the synthetic process(es) is not describing all the manufacturing steps and critical process parameters. Unacceptable starting materials (not as per ICH Q11) e.g. Azithromycin dihydrate -> Azithromycin trihydrate (as a single step)
3.2.S.2.1 Manufacturer and address	Manufacturer and address
3.2.S.2.3 Control of raw materials	• Absence of control of all raw materials. Details concerning API starting materials preparation is insufficient or missed.
3.2.S.2.5 Process validation and/or evaluation	• Process Validation of API aseptic processing and sterilization is not submitted.
3.2.S.3 CHARACTERISATION	
3.2.S.3.1 Elucidation of structure and other characteristics	• Not all Essential Techniques are performed. Chromatograms, spectrum or thermograms are not provided or not clear. Enumerated Structure for NMR is not submitted. Particle size distribution data for BCS Class II, Class IV and unknown/unclear BCS Class APIs used to manufacture non-solution oral dosage forms not provided.
3.2.S.3.2 Impurities	• Potential impurities are not discussed, especially for non-pharmacopeial API. Excluding identified impurities specified in an official compendial monograph and are not controlled by the proposed routine in-house analytical procedure without Justification. Setting Acceptance criteria for impurities exceeding ICH Q3A guideline Acceptance criteria without justification. Carry over impurities from starting material are not discussed. Elemental impurities and Genotoxic impurities Risk assessment are missing. Residual solvent risk assessment for solvents used early in manufacturing process and aren't controlled in the specifications. Risk assessment for benzene as impurity in solvents is missing.

Human & Veterinary Dossiers

COMMON SCREENING DEFICIENCIES

3.2.S.4 CONTROL OF API	
3.2.S.4 .1 Specifications	• Absence of API and/or FPP manufacturer's API specifications (used in routine testing of API) • Absence of signed, dated and version-controlled specifications • Absence of test and limits for benzene where applicable
3.2.S.4.2 Analytical Procedures	• Absence of API and/or FPP manufacturer's API analytical procedures • Absence of signed, dated and version-controlled specifications
3.2.S.4.3 Validation of analytical procedures	• Absence of API and/or FPP manufacturer's API validation of analytical procedures • Absence of signed, dated and version-controlled specifications
3.2.S.4.4 Batch analysis data	• Recent batch analyses of at least two batches are not submitted. • Absence of batch analysis of API batch used to manufacture the clinical batch or bioequivalence batch
3.2.S.7 Stability	•
3.2.S.7.1 Stability Summary and Conclusions	• Failure to propose shelf-life/retest period and storage conditions
3.2.S.7.2 Post – approval Stability Protocol and Stability Commitment	• Absence of signed and dated post-approval stability commitment letters. • Absence of authorized post-approval stability protocol
3.2.S.7.3 Stability data	• Absence of Up-to-date stability results and update the summary of stability. • Absence of the ongoing stability study for the recent batches. Please note: The minimum data for API required at the time of submitting the dossier are as follows:

	Storage temperature(°C)	Relative humidity (%)	Minimum time period (months)
1. Accelerated	40±2	75±5	6
2. Intermediate *	-	-	-
3. Long-term	30±2	65±5 or 75±5	6

*Where long-term conditions are 30°C±2°C/65%±5%RH or 30°C±2°C/75%±5%RH, there is no intermediate condition.

Refer to WHO Technical Report Series, No. 953, Annex 2 for further information regarding the storage conditions, container closure system, test specifications and testing frequency.

Human & Veterinary Dossiers

COMMON SCREENING DEFICIENCIES

3.2.P Drug product (P part)	
3.2. P.1 Description and Composition of the Drug Product	• Inconsistent description with that provided in the MC8 application form, specifications, samples, and labelling information.
3.2. P.2 Pharmaceutical Development	• Absence of comparative dissolution data Absence of studies demonstrating discriminatory nature of a dissolution method.
3.2.P.2.3 Manufacturing Process Development	• Absence of justification for selection of sterilization process. *For sterile products (* *Filter-drug product compatibility studies* *Filter microbial retention studies* *Filter integrity studies*
3.2.P.2.6 Compatibility	• Absence of compatibility with diluent, medical devices (not API – excipient) if it not mentioned in the stability.
3.2.P.3 Manufacture	
3.2.P.3.1 Manufacturer(s)	• Absence of discussion for the responsibility of each manufacturer involved in the manufacturing process of the FPP. Addresses of manufacturing sites do not include blocks or units.
3.2.P.3.3 Description of Manufacturing Process and Process Controls	• Holding time is not specified and supportive stability data is not submitted.

COMMON SCREENING DEFICIENCIES

3.2.P.3.5 Process Validation and/or Evaluation	• **Absence of Process Validation on 3 primary batches. (If applicable)**
	• **Process validation of all batch sizes is missing.**
	• **For sterile products:**
	  ○ **Manufacturing process validation**
	  ○ **Media fill studies**
	  ○ **Validation of sterilisation of vials, rubber bungs, etc**

3.2.P.4 Control of Excipients	
3.2.P.4.1	• Absence of specifications of the in-house excipients.
3.2.P.6 Reference Standards or Materials	• **Absence of COA of working RS, Lot number of the primary RS that was standardized against it and IR of the primary RS and secondary RS run concomitantly in case of using working RS .**
3.2.P.7 Container Closure System	• Absence of Identification spectrum (IR) of reference and test packaging materials. • Absence of chemical test for aluminium in specifications
3.2.P.5.1 Specification(s)	• Absence of FPP manufacturer's release and shelf-life specifications (used in routine testing of API). • Absence of signed, dated and version-controlled specifications
3.2.P.5.3 Validation of Analytical Procedures	• Absence of FPP manufacturer's validation of analytical procedures • Absence of signed, dated and version-controlled specifications

COMMON SCREENING DEFICIENCIES

3.2.P.6 Reference Standards or Materials	• **Absence of COA of working RS, Lot number of the primary RS that was standardized against it and IR of the primary RS and secondary RS run concomitantly in case of using working RS .**
3.2.P.7 Container Closure System	• Absence of Identification spectrum (IR) of reference and test packaging materials. • Absence of chemical test for aluminium in specifications
3.2.P.8 Stability	
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment	• Absence of signed and dated post-approval stability commitment letters. • Absence of authorized post-approval stability protocol
3.2.P.8.3 Stability Data	• Absence of Up-to-date stability results • Absence of the ongoing stability study for the recent batches. • Absence of in use stability study. • Absence of long-term stability data for vials in inverted position (sterile products). • Please note: The minimum data of FPP required at the time of submitting the dossier are as follows:
3.2.R Regional Information	
3.2.R.1 Production documents	
3.2.R.1.1 Executed production documents	• Absence of the production batch record of the manufactured three batches • Absence of production documents for bio batch and biowaiver batches.
Module 5	
5.3.1 Bioequivalence Studies	The following bioequivalence data are commonly absent from submissions: • Absence of the following documentation • Comparator product source and storage conditions • COA for reference and test product • GCP, GLP • Bioanalytical method and bioanalytical method validation Please note that all documents must be indexable and searchable.

	Storage temperature (ºC)	Relative humidity (%)	Minimum time period (months)
Accelerated	40±2	75±5	6
Intermediate *	N/A	N/A	
Long-term	30±2	65±5**	12

*Where long-term conditions are 30ºC±2ºC/75%±5%RH, there is no intermediate condition.
** Stability studies conducted at 75% relative humidity are also acceptable

Human & Veterinary Dossiers

COMMON SCREENING DEFICIENCIES

Cover letter	• Absence of signed and dated cover letter that includes the full details of the local representative, and this should have included the full name and email address of the responsible person.
CM1 form	• Incomplete, not signed, and dated CM1 form with incomplete details for example complete address of the principal and name of manufacturer.
Declaration by the applicant	• Absence of signed and dated declaration by the applicant attesting to the accuracy of the contents of the application.
Proof of compliance with current Good Manufacturing Practices (cGMP)	• Absence of valid cGMP certificates manufacturers issued by a governmental organisation not an accrediting or quality assurance company
Excipients	• Formulations containing restricted excipients (preservatives e.g. bronopol)
Document control	• CoAs, specifications are not signed dated, or version controlled.
Labelling (primary and secondary packaging)	• Incorrect labels that not consistent with the requirements of S.I 97 of 2015 and Complementary medicines guidelines
Package insert and patient information leaflet	• Incorrect package inserts S.I 97 of 2015 and Complementary medicines guidelines • Absence of the package insert
Stability	• Absence adequate stability data to support the proposed shelf life.

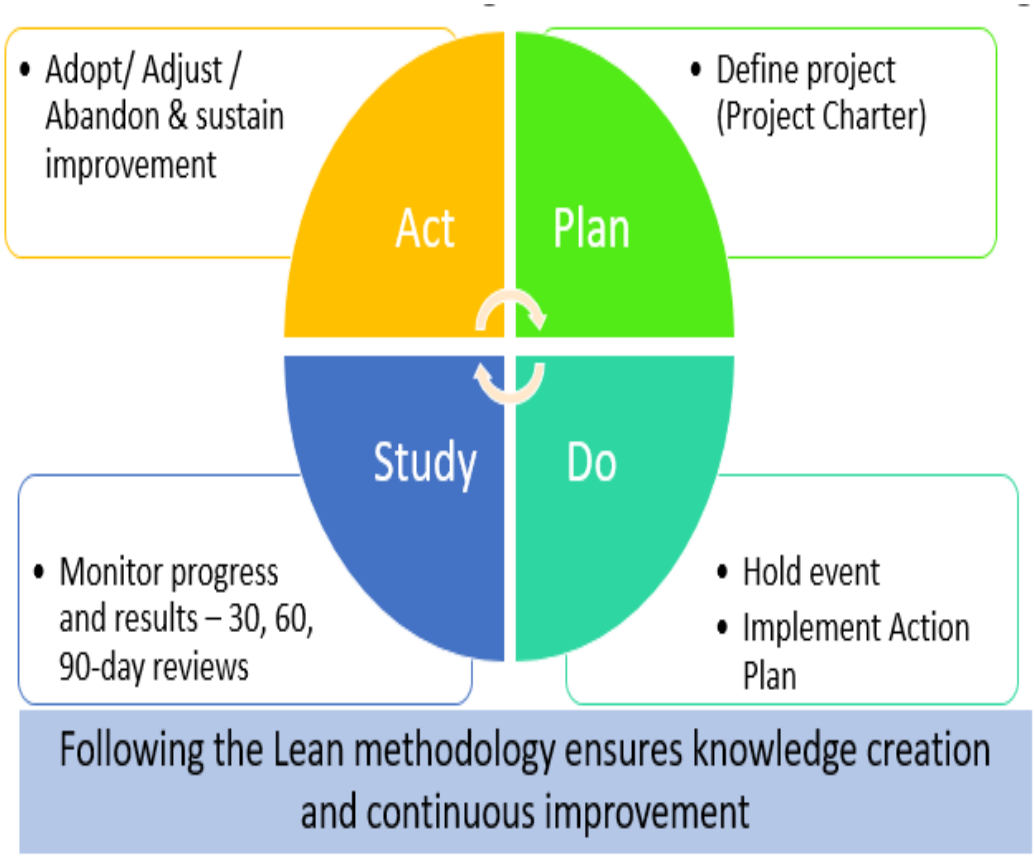
Complementary Medicines Dossiers

CHALLENGES

- Lean Human Capital
- Tight Deadlines [*10 working day screening timeline, 60 calendar day evaluation 1st and 2nd Evaluation deadlines*]
- Delays in automation
- Staff Attrition
- Submission of Grossly deficient applications for registration
- Increase in submissions indicating growth in pharmaceutical sector
- Challenges in local manufacturing facilities attaining acceptable cGMP status

Way Forward

The Lean Methodology



Thank you for your attention!