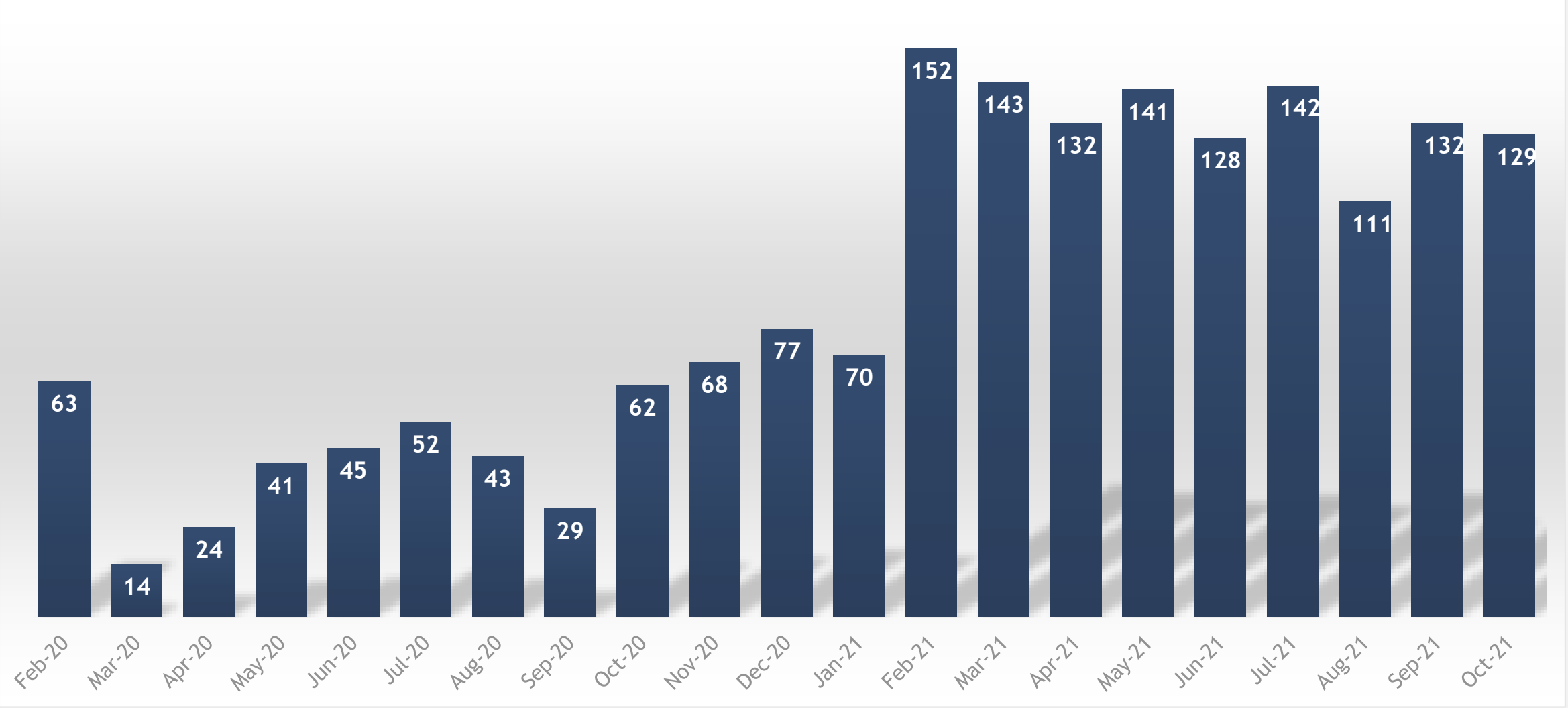
SAHPRA
South African
Health Products
Regulatory Authority

Backlog Clearance Project Performance Update

SAPRAA Meeting
18 November 2021

New Registration Applications

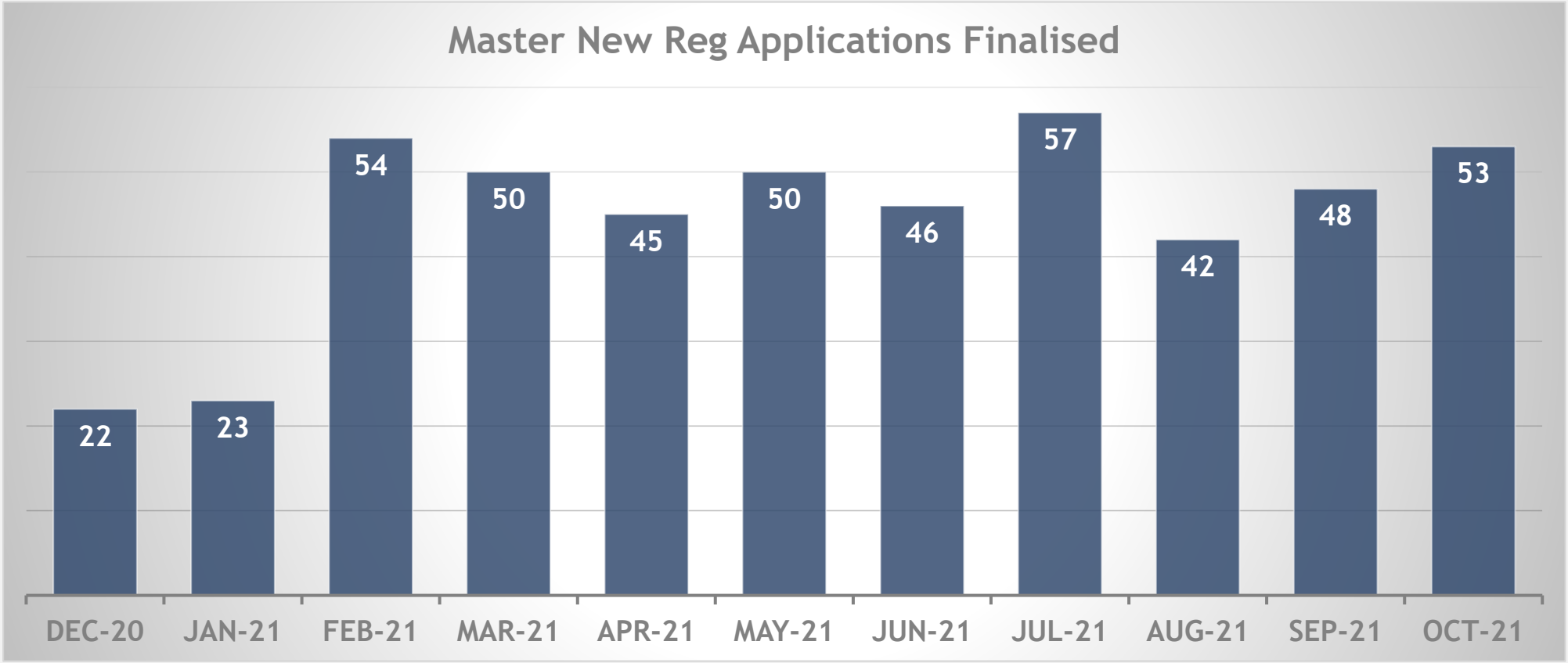
New registration applications finalized (line items) since start of the Backlog Clearance Programme



Currently 92 for Nov 2021

New registration applications finalized (master applications) since December 2020

Since Feb 2021, an average of 49 masters/month cleared



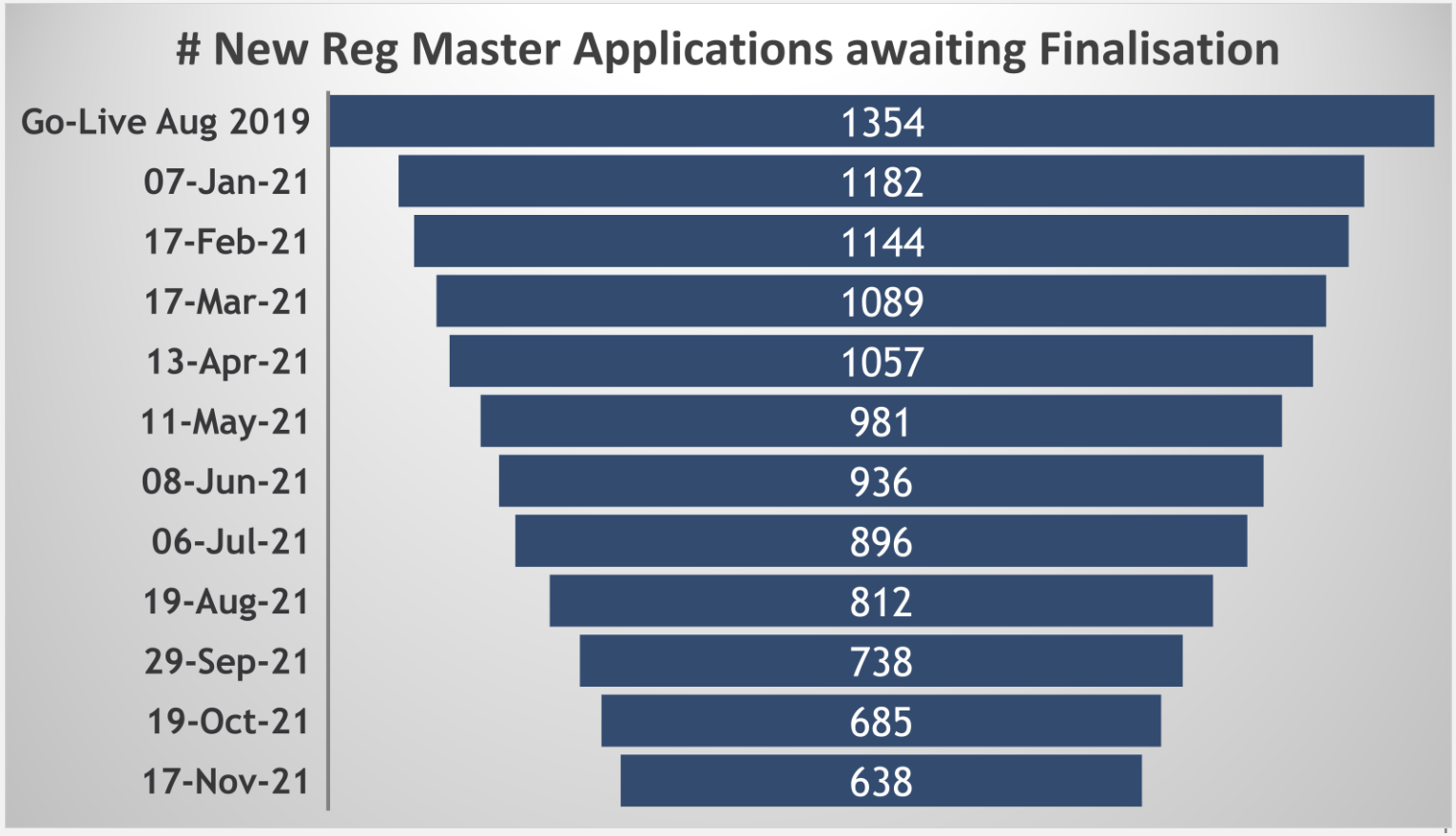
Currently 36 for Nov 2021

Data as of 17 Nov 2021

Clearance of New Registration Applications

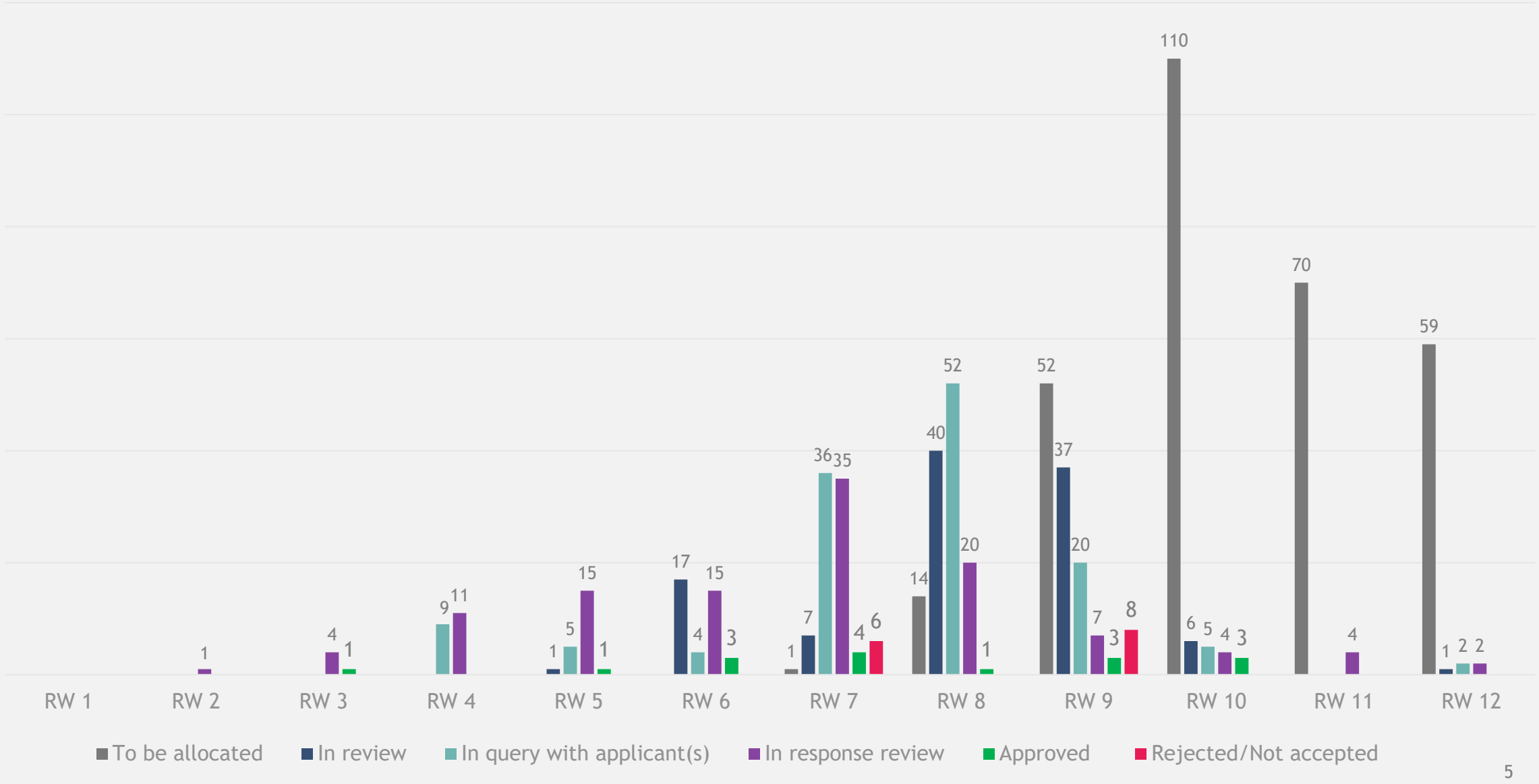
172 master applications cleared in 2020
544 master applications cleared since January 2021

> 670 master applications registered since Go-Live on 01 Aug 2019



Evaluation – In progress

Data as of 09 November 2021



Variation Applications

Distribution of variations across end-to-end process

Current status

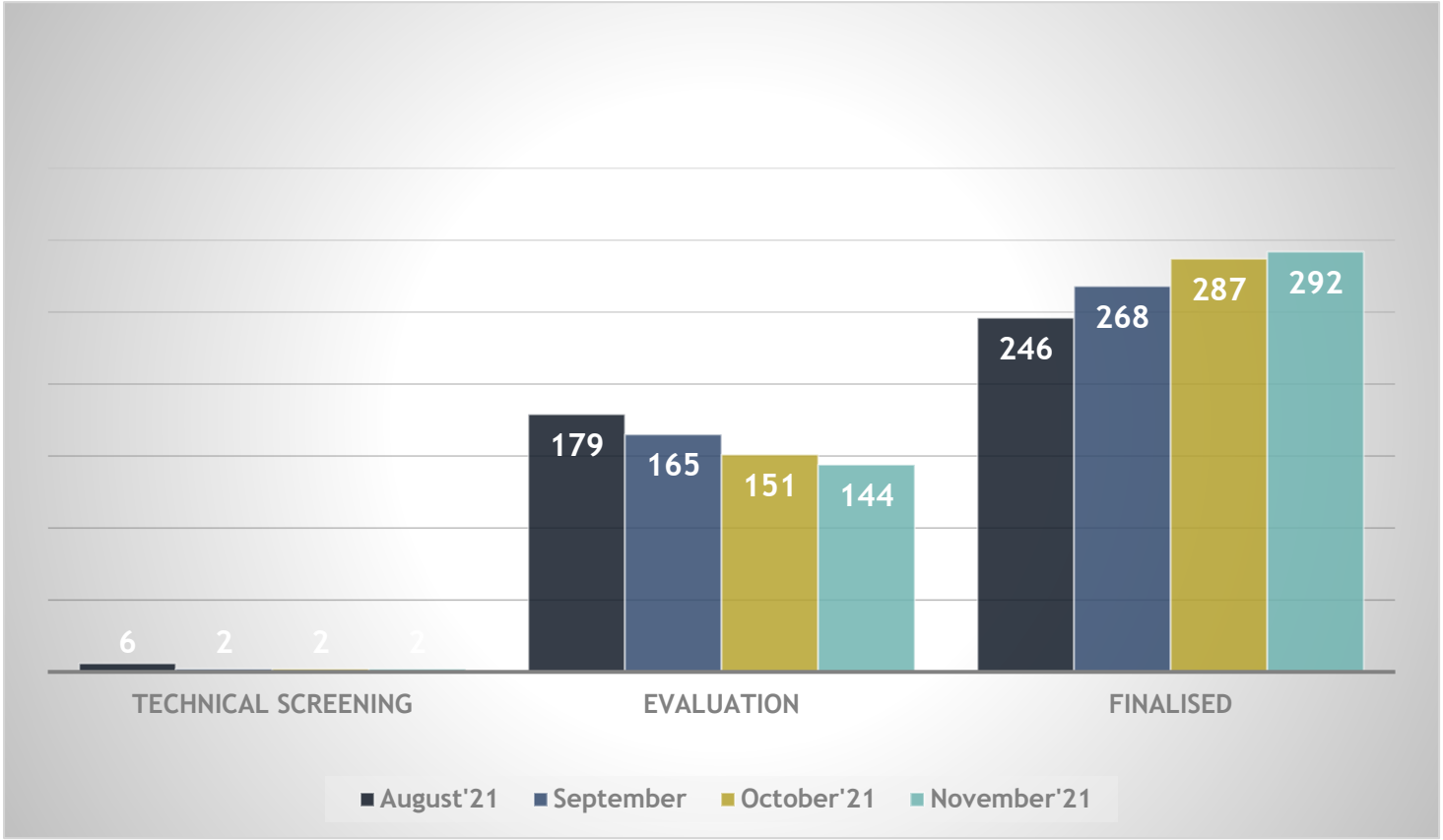
Date as of 9 November 2021

	Admin screening[2]	Technical screening	Evaluation	Approved or rejected[3] Withdrawn/Rejection/Non-Approvals*	Sum
Today	0	2	148	251 (41)	= 442
P&A	0	0	11	130	
Clinical	0	2	125	96	
Inspectorate	0	0	0	8	
Multiple[4]	0	0	12	17	
Withdrawn/Rejection/Non approval	0	0			

1. Number of type II variation codes associated with the application 2. Compliance check, A.2 technical validation and A.3 business validation; 3. Applications have been approved for registration or rejection by SAHPRA RC. Certificates may not yet be generated and/or issued 4. Applications have a code relevant to multiple units, or multiple codes relevant to multiple units.

* Withdrawn/Rejection/Non-Approvals

Monthly Progress - Variations



- Total of **442** variations

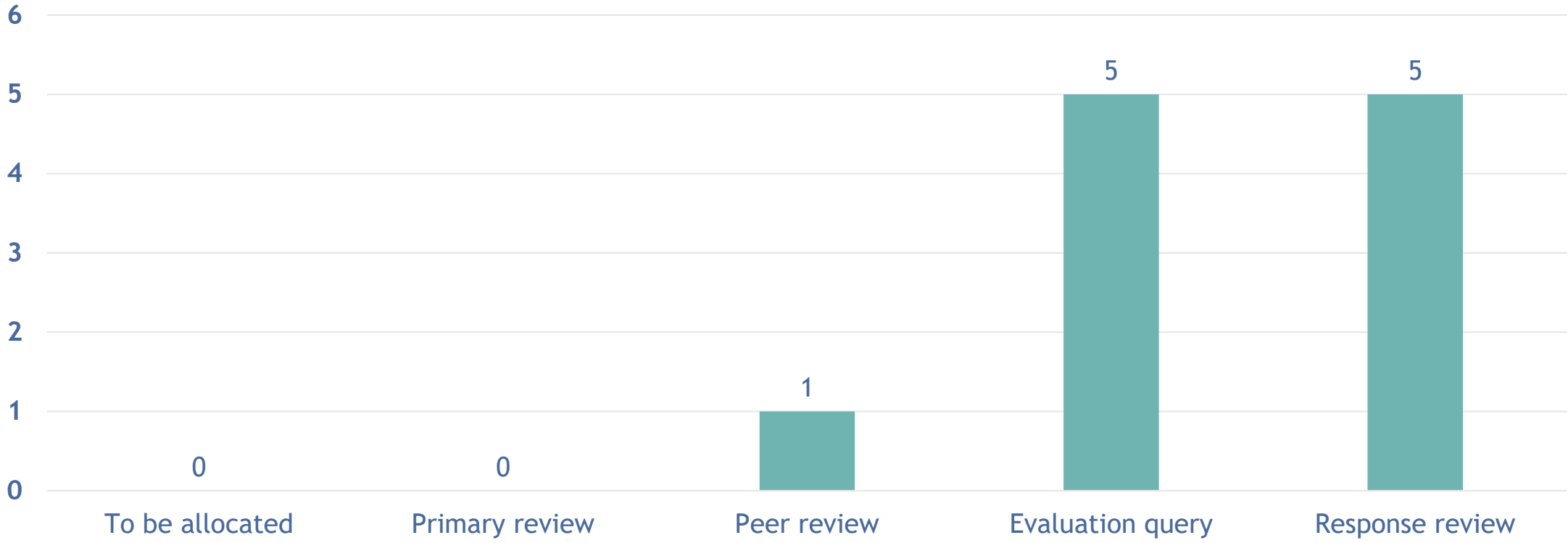
- **66%** variations finalised* to-date (including withdrawals and non-acceptances)
- **34%** still to be finalised

- Breakdown of outstanding **34%:**
  - **87%** - Clinical NCEs (safety updates and new indications)
  - **8%** ME&R
  - 0% Inspectorate
  - **5%** Multiple

*Finalised = approvals & withdrawals/non-approvals

P&A Variation Deep Dive

P&A outstanding - 8%



Clinical Variation Deep Dive

Clinical outstanding - 87%

Interventions

Interventions in Backlog

Quality/Bio-Equivalence:

A. Abridged Review Pathway for certain Quality (Q)/Bio-Equivalence (BE) sections of dossiers (unredacted assessment reports available for ~300 applications)

B. Q/BE Internal Reliance: Batch processing of applications, e.g. similar Active Pharmaceutical Ingredient (API) manufacturers, Drug Master Files (DMFs), Final Pharmaceutical Product (FPP) manufacturers, BE studies, etc.

C. Q/BE Risk-based assessment pilot study

Clinical:

D. Clinical Internal Reliance: Professional Information (PI) templates generated by Clinical Unit for supermolecules

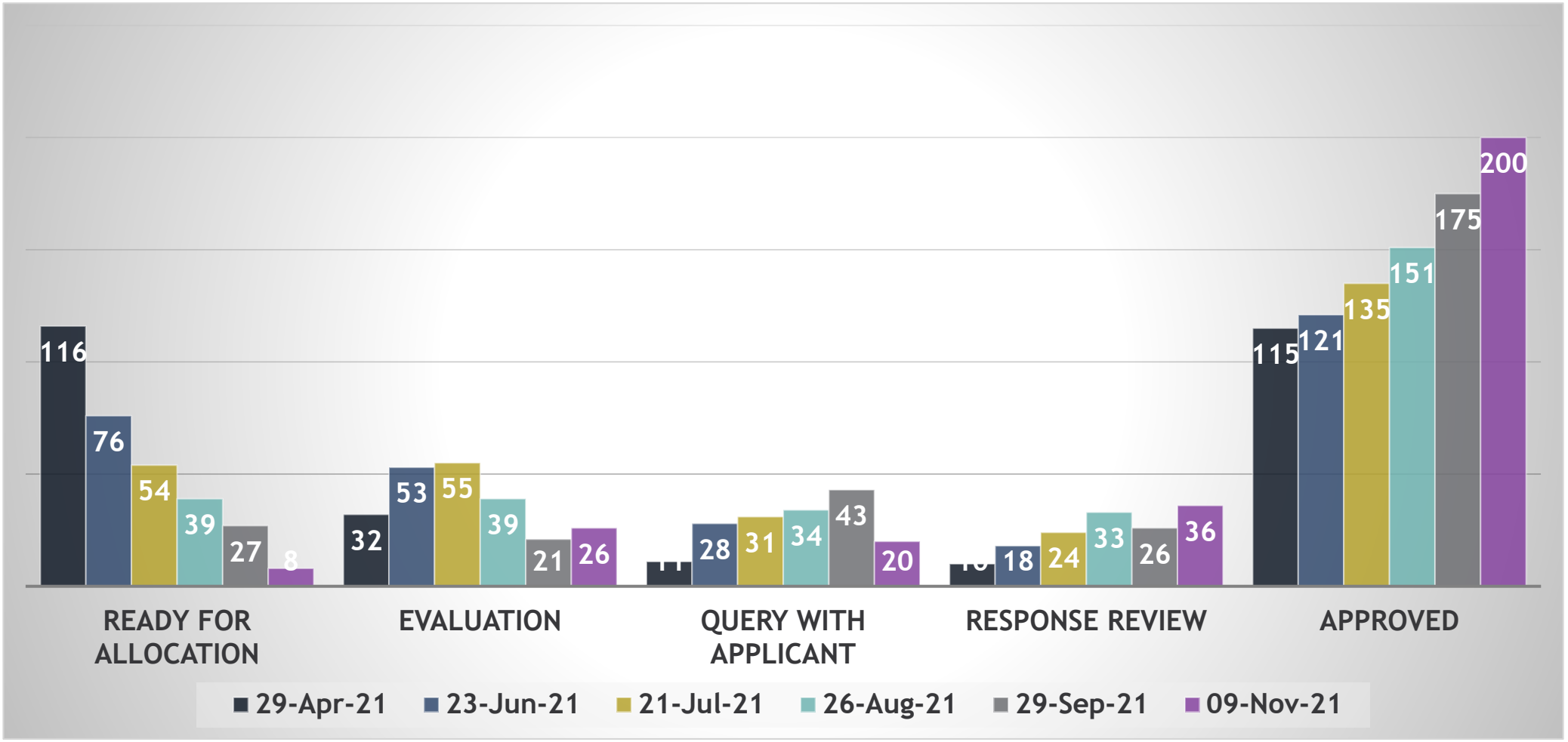
E. Clinical Risk-based assessment pilot study

Cross-utilisation of all above interventions in order to expedite a specific application.

A. Abridged Review Pathway for Quality/Bio-Equivalence sections of certain dossiers

Data as of 09 Nov 2021

32 % left to finalise (90/290 master applications)



B. Q-BE Internal Reliance - Batch Processing

	Available for allocation	Abridged/Verified Review Pathway	Full Review Pathway	Batch processing possible for full review applications*
RW8	89	8	81	**50/81**
RW9	102	14	88	**53/88**
RW10	113	26	87	**61/87**
RW11	68	10	58	**34/58**
RW12	56	6	50	**32/50**

*Batch processing may be applied to these applications, as these are either identical applications, or share the same active pharmaceutical ingredient and/or final product manufacturers, the same Drug Master Files (DMF) or Bio-Equivalence (BE) studies.

C. Q & BE Risk-Based Assessment Pilot Study

- Pilot study commenced on 20 September 2021.
- The risk-based pilot study was initiated with 63 generic master applications (Resubmission Window 8 Full Review applications - Analgesics), which were classified according to the developed risk-decision trees and tables at screening stage.
- The classifications identified 43 applications as low risk and 20 applications as high risk. Different assessment templates are used for low- and high-risk products (each template combines validation and assessment in order to reduce admin burden on evaluators).
- Batch processing of applications was conducted, which allowed for easy identification of applications with commonalities w.r.t API, DMFs, FPP, Biostudy, etc., enabling strategic allocations.
- Bulk allocations are done where evaluators (cohort of 10 comprising in-house SAHPRA, external domestic & international evaluators) receive 1-3 applications per week, depending on available hours.

Weekly Peer Review Sessions

Week	Peer Review Sessions	# of Applications Tabled
1	04 October 2021	5 applications (peer review)
2	11 October 2021	13 applications (peer review)
3	18 October 2021	11 applications (peer review)
4	25 October 2021	7 applications (peer review) + 2 response reviews
5	03 November 2021	9 applications (peer review) + 4 response reviews
6	11 November 2021	10 applications (peer review) + 2 response reviews
7	18 November 2021	4 applications (peer review) + 9 response reviews

Average time for peer review meetings: ~2-3 hours, but dependent on number of applications to be discussed.

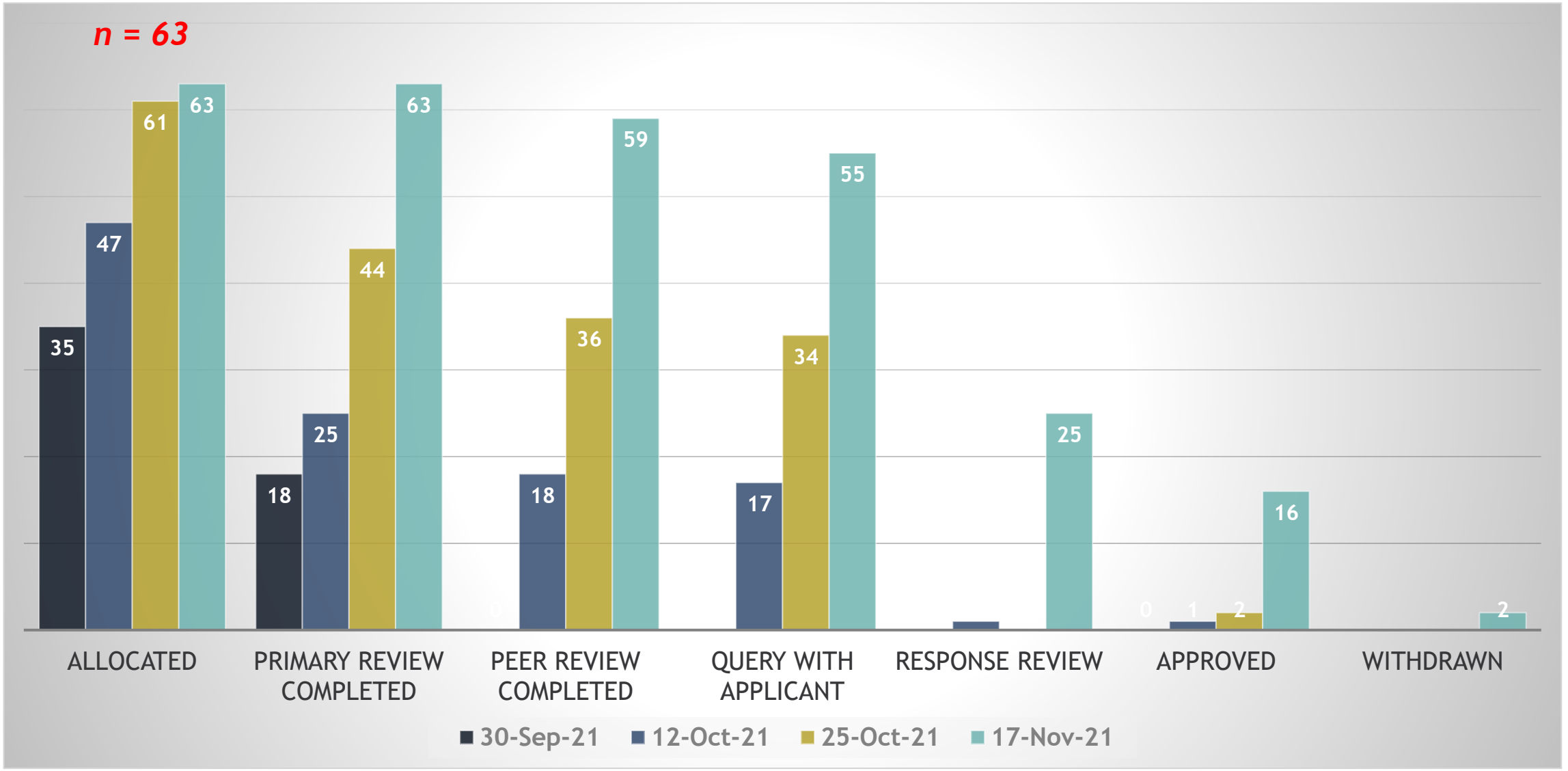
The documents are compiled and shared on Google Docs in advance to allow evaluators to provide their comments - the living document shows all comments in real time, allowing all evaluators to see each other's comments. This has greatly reduced the peer review session times since comments are made before the meeting and therefore addressed either before or during the meeting session.

Applicant Responses

- Applicants given 10 working days to respond due to only critical queries raised. Much shorter timeframe compared to 20 working day response timeline currently in Backlog.
- Applicant extension requests to submit responses have been received for ~ 12 applications.
- Extension requests granted in these cases; sometimes after engagement with applicant to clarify queries, as well as for SAHPRA Backlog to understand applicant challenges.
- Applicants indicated that generally 20 working days would be sufficient time for them to collect the data from the manufacturers as they are currently understaffed due to COVID-19, delays due to country holidays and generation of the data required.
- Generally, extension requests in Backlog are > 1-3 months from due response date. The extension requests for the pilot study applications are dramatically reduced.

Current Q-BE Status of Pilot Study Applications

Data as of 17 Nov 2021



Conclusion

Data as of 17 Nov 2021

- After **43** working days since commencement of the pilot study:

  = 100 % applications completed primary review
  = 94 % of the applications peer reviewed
  = 87% queries sent out to the applicants
  = 40 % in response review
  = 29 % Q & BE approved/withdrawn

- Other units' progress (i.e Inspectorate, Naming & Scheduling and Clinical) is monitored in order to ensure expeditious finalisation of applications.

- Outcomes of pilot study to be assessed for feasibility of this approach for the Backlog Clearance Programme and SAHPRA in general.

D. Clinical Internal Reliance: PI/PIL Templates

Resubmission Window	PI/PIL Templates for Supermolecules (APIs)
RW8	APIs: Tramadol, paracetamol+tramadol, celecoxib, paracetamol, ibuprofen, ibuprofen+paracetamol, ibuprofen+orphenadrine+paracetamol; acetylsalicylic acid; acetylsalicylic acid+caffeine+paracetamol; diclofenac
RW9	APIs: Pregabalin, sildenafil, solifenacin, rizatriptan, rasagiline, levetiracetam, gabapentin
RW10	APIs: Drosperinone, ethinyl estradiol, Levonorgestrel, esomeprazole, pantoprazole, ondansetron, desogestrel+ ethinyl estradiol, octreotide, finasteride, ethinyl estradiol+gestodene
RW11	APIs: Zoledronic Acid, Brimonidine, Timolol, Colchicine, Dexamethasone, Tobramycin, Dorzolamide, Timolol, Latanoprost, Timolol, Povidone Iodine, Raloxifene
RW12	APIs: 2,4-Dichlorobenzyl Alcohol, Amylmetacresol, Azelastine, Mometasone Furoate, Desloratadine, Levocetirizine, Levocetirizine & Montelukast, Olopatadine

E. Clinical Risk-Based Assessment Pilot Study

Data as of 17 Nov 2021

- Retrospective Study: Commenced with pilot study in week of 20 September 2021
- 3 New Chemical Entity (NCE) New Registration Applications selected from applications already concluded by Backlog (brexpiprazole, tofacitinib & venetoclax)
- Cohort of 3 Clinical evaluators selected (1 x external domestic, 1 x external regional & 1 x International evaluator)
- Introductory meetings between Centre for Innovation in Regulatory Sciences (CIRS), SAHPRA Clinical Unit & evaluators to discuss CIRS' UMBRA* Framework
- Evaluators each allocated one NCE to pilot (together with the SAHPRA assessment reports)
- All completed UMBRA templates returned by evaluators
- Next step: Pilot study outcome discussions between 3 pilot study evaluators, SAHPRA Advisory Clinical Committee Chair and CIRS
- Prospective study: BAU

* Universal Methodology for Benefit-Risk Assessment

Q&A