PARTIAL MINUTES OF 317th MEETING OF REGISTRATION BOARD HELD ON 16th & 17th MAY, 2022.

==*=*=*

317th meeting of Registration Board was held on 16th- 17th May, 2022 in the Committee Room of Drug Regulatory Authority of Pakistan, G-9/4, Islamabad. The meeting was scheduled up to 18th May, 2022 but was concluded on 17th May, 2022. The meeting was chaired by Dr. Obaidullah, Director, Pharmaceutical Evaluation & Registration Division, DRAP. The meeting started with recitation of the Holy Verses.

The meeting was attended by the following: -

1.	Dr. Rafeeq Alam Khan, Meritorious Professor, Faculty of Pharmacy, Ziauddin University, Karachi.	Member
2.	Dr. Qurban Ali, Former Director General, National Veterinary Laboratories, Islamabad	Member
3.	Dr. Ali Ahmed Agha, Director, Drugs Testing Laboratory, Quetta. Government of Balochistan	Member
4.	Syed Adnan Rizvi, Director, Drugs Testing Laboratory, Karachi Government of Sindh	Member
5.	Dr. Imranullah Khan, Director, Drugs Testing Laboratory, Peshawar Government of KPK	Member
6.	Mr. Muhammad Aslam, Deputy Draftsman-II, Representative of Ministry of Law & Justice, Islamabad	Member
7.	Mr. Ghulam Mujtaba, Deputy Director, Representative of IPO, Islamabad.	Member
8.	Ch. Zeeshan Nazir, Additional Director, Representative of Biological Evaluation & Research Division, DRAP	Member
9.	Mst. Mahvash Ansari, Deputy Director, Representative of QA&LT Division, DRAP	Member
10.	Mr. Abdullah, Additional Director (PE&R), DRAP.	Member/ Secretary

Mr. Muneeb Ahmed Cheema DD, Mr. Asif Jalil, Incharge PEC, Hafiz M. Ali Tayyab AD, Noor-ul-Ain Arshia AD, Sana Kanwal AD, M. Sarfraz Nawaz AD and respective Assistant Directors of PE&R attended the meeting to present the agenda of PE&R Division. M. Zubair Masood AD, M. Kashif AD & Mr. Saadat Ali Khan AD attended the meeting to present agenda of DBER. Deputy Director, QA&LT was assisted by respective Assistant Directors to present the agenda of QA&LT Division.

Mr. Jalal Ud Din Zaffar & Mr. Hamid Raza (PPMA); Mr. Nadeem Alamgir (Pharma Bureau) and Mr. Zia-ul-Haq & Mr. Saif-ur-Rehman (PC&DA) attended the meeting as observers.

Item No. II Division of Pharmaceutical Evaluation & Registration

Registration-I Section

Case No.1. Personal Hearing Notices Issued to Registration Holders of Diclofenac Potassium 75mg & 100mg Tablet/ Capsule.

1. Registration Board, in its various meetings considered the case regarding *"Registration Status of Formulations (Diclofenac Potassium 75mg & 100mg and Famotidine 10mg/5ml) not approved by Reference Regulatory Authorities & Previous Decisions Taken by the Registration Board in its 250th & 258th Meeting".*
2. With respect to "Diclofenac Potassium", complete record including proceedings & decisions of Registration Board and relevant decisions of DRAP's Authority have been reproduced as under:

Sr. No.	Formulation	Ref. Meeting No. of RB	Decision/Remarks
1.	Diclofenac Potassium 75mg & 100mg	M-258 *(held on 25th-26th April, 2016)*	**Decision:** Diclofenac Potassium is not registered in any reference country in dose more than 50mg, thus Registration Board decided to issue show cause notices to manufacturers of Diclofenac Potassium (75 and 100mg) for de-registration of these products.

3. **Current Status of WP No 1695/2017**

M/s. Quaper Pharmaceuticals (Pvt) Limited, Sargodha has filed a Writ Petition in Islamabad High Court Islamabad v/s Federation of Pakistan, Drugs Registration Board etc against issuance of show cause notice in the case of Diclofenec Potassium 75mg Tablets. The case was heard on 30-05-2017and adjourned. ***The Islamabad High Court, Islamabad dismissed the application of M/s. Quper Pharma, Sargodha vide its orders dated 29-01-2020 being without merit.***

4. ***Decision of M-288 held on 14th-15th Feb, 2019:***

Registration Board decided that all registration holders of "Diclofenac Potassium 75mg & 100mg" shall be called for personal hearing.

5. ***Decision taken by DRAP's Authority in its 70th meeting held on 05th Sep, 2019:***

For formulations containing "drugs" which were previously registered by the Registration Board and have proof of availability and prescription of last 10 years but are not available in the Reference Regulatory Authorities shall continue to be considered/ registered as drugs until and unless withdrawn on Safety, Efficacy and Quality reasons.

6. ***Decision of M-296 held on 08th-10th Sep, 2020:***

Registration Board deliberated the case in the light of above stated facts / opinions and decided as under:

i. *Since, all such formulations which are not approved by the Reference Regulatory Authorities; the safety and efficacy profile cannot be established in the absence of a well-established system for reporting of adverse events, so a reference shall be forwarded to DRAP's Authority with the request to review the decision taken in its 70th meeting held on 05-09-2019. In this regard, PE&R Division shall prepare a comprehensive document/agenda for consideration of Authority, keeping in view the practices adopted by RRA for all such formulations;*
ii. *For all those formulations which are registered/ applied in strengths, different from those approved by reference regulatory authorities, the registration holders/ applicants shall standardize their formulations (by submitting registration application with requisite fee, provided that the firm did not have same registration) in line with those approved by reference regulatory authorities. In this regard, recommendation shall be forwarded to DRAP's Authority to exempt all such*

cases/applications for standardization of formulation to be submitted on Form-5F/CTD format as notified vide SRO 713(I)/2018 dated 09-06-2018.

iii. *Drug products withdrawn from RRA due to any commercial reason shall be considered for registration by Registration Board.*

iv. *Vitamin-mineral formulations will be considered as per vitamin policy approved by Policy Board and further adopted by Registration Board in its 295th meeting.*

Keeping in view the point (i) and in order to proceed further for effective implementation/ execution of point (ii) to (iv) of the above-mentioned decision, the Authority was requested to review the decision taken vide its 70th meeting held on 05-09-2019.

7. *Decision of DRAP Authority in its 125th meeting held on 03rd Nov, 2021:*

The Authority deferred the agenda item for detailed deliberations keeping in view the therapeutic categories etc. of such formulations.

8. Proceedings of M-313:

i. The concept of reliance on the decisions of reference regulatory authorities adopted by the Registration Board in its 275th meeting was reiterated as deliberated during proceedings of 296th meeting with respect to instant case.

ii. Furthermore, Registration Board was apprised that a policy of reliance on reference regulatory authorities has also been approved by the Authority in its 73rd meeting held on 06-11-2019.

iii. Registration Board was also informed regarding court case (CP No.1545/2017) filed by M/s Cibex (Pvt.) Ltd., Karachi vs DRAP & others i.e, sub-judiced before the hon'ble Sindh High Court and written statement/updated registration status of such formulations on behalf of DRAP is required to be furnished.

iv. It was further deliberated that relevant registration holders/ manufacturers shall be provided with an opportunity to submit their response regarding (a) evidence for approval status of such formulation in reference regulatory authorities (b) product development data and relevant studies with respect to quality, safety and efficacy of these formulations.

9. Decision of M-313 held on 16th-18th Nov, 2021:

Keeping in view the detailed deliberations during proceedings of its 296th and 313th meeting, Registration Board decided as under:

i. *To issue show cause notices to all registration holders/ manufacturers (including those listed in above tables) of below mentioned formulations under Section 7 (11)(d) of the Drug Act, 1976 that why the registration of their products may not be cancelled in the public interest. In this regard, the Board advised relevant registration sections to review the above-mentioned lists for correctness and issue notices accordingly. Moreover, any registration holder not included in above lists shall also be issued show cause notice after approval of Chairman Registration Board.*

ii. *Furthermore, management of these firms shall also be given the opportunity of personal hearing in the forthcoming meeting of the Board under section 42 of the Drugs Act, 1976.*

S. No.	*Formulations*
1.	*Diclofenac Potassium Tablets/ Capsules in strengths greater than 50mg*
2.	*Famotidine Suspension in strength/dosage form other than 40mg/5ml Powder for Oral Suspension.*

iii. *The Board also advised to share the updated status with hon'ble Sindh High Court if required.*

10. Decision of 128th meeting of Authority held on 14th Dec, 2021:

I. The Authority endorsed the recommendations of Registration Board and made following decisions:-

A. *Partially reviewed its earlier decision taken in its 70th meeting held on 05-09-2019, consolidated amended decision is reproduced as under:*

1. *For molecules falling in the grey areas or overlapping between PE&R and H&OTC division:*
    a. *Formulations/molecules already registered as "drugs" by Registration Board shall continue to be considered / registered as drugs irrespective of their status in Reference Regulatory Authorities until and unless withdrawn on Safety, Efficacy and Quality reasons.*
    b. *If any such formulation was also enlisted by H&OTC Division, it will be un-enlisted. The applicants shall be advised to approach PE&R Division for processing of application for registration. For such un-enlisted applications, a separate queue shall be prepared by the PE&R Division in order to avoid discomfort to the applicants and assurance of availability of such formulations for patients.*
    c. *This decision shall not apply to those formulations / molecules covered under Vitamin-Policy as approved by the Policy Board.*
2. *New formulations/molecules other than those which were already registered by Registration Board will be considered on the basis of their status in Reference Regulatory Authorities. If in the RRA, these are considered as drugs, these will be dealt by the PE&R Division while otherwise will be dealt by Health & OTC Division.*
3. *Endorsed the Reference Regulatory Authorities as adopted by the Registration Board from time to time and the criteria being opted to adopt RRAs. Registration Board was advised to issue a notification of adopted RRAs and comprehensive selection criteria for information and easy understanding of all relevant stakeholders.*
4. *Drug formulations/strengths which were previously registered by the Registration Board but are not available in any Reference Regulatory Authorities, shall be reviewed and disposed off keeping in view of safety and efficacy evidence / data in the Reference Regulatory Authorities.*

B. *Registration Board may decide and dispose off such formulations as and when identified/reported.*

II. *The Authority further advised Registration Board to review existing RRAs for veterinary drugs and submit its recommendations to the Authority for its consideration.*

11. In line with the decision taken by the Board in its 313th meeting, show-cause/personal hearing notices were issued to **162** registration holders for hearing before the Registration Board on 1st February, 2022 at 10 a.m. (for Diclofenac Potassium) & 2.30 p.m (for Famotidine). However, due to prevailing cases of COVID-19, personal hearings have been postponed (vide letter issued dated 27-01-2022).

12. **<u>Current Status of CP No.1545/2017 filed by M/s Cibex in SHC [Catafen 100 Tablet (Diclofenac Potassium 100mg) Reg. No.039198:</u>**

M/s Cibex (Pvt.) Ltd., Karachi has also filed a court case against DRAP and others for issuance of letter [regarding change in registration status of Catafen Tablet 100mg (Diclofenac Potassium; R#039198) from M/s Macter to M/s Cibex]. The last date of hearing was Friday, 28th January, 2022 wherein *"Syed Hakim Masood, Federal Inspector Drugs, DRAP, Karachi present and undertakes that the Petitioner's grievance including the other items will be considered in the forthcoming meeting which will probably be held on or about 01.02.2022. In the wake of above, the matter is adjourned to 04.03.2022."*

13. **<u>Writ Petition No. 365/2022 filed by M/s Siza International Private Limited, Lahore [Rheumatin-K Tablet (Diclofenac Potassium: 75me) Reg. No. 024049]:</u>**

Operative part of court order dated 07-01-2022 is reproduced as under:

"Subject to notice in the meanwhile proceedings under the impugned show cause notice dated 29th of December, 2021 shall continue but the final decision shall not be made till the next date of hearing"

14. **Writ Petition No. 4168/2022 filed by M/s Shrooq Pharmaceuticals (Pvt) Ltd., Lahore [Pointer 75 Capsule (Diclofenac Potassium (Pellets): 75mg) Reg. No. 064791 & Moven-75mg Tablet (Diclofenac Potassium: 75mg) Reg. No. 040304]:**

Operative part of court order dated 24-01-2022 is reproduced as under:

"At the outset learned proxy counsel submits that since identical matter (W.P. No. 365/2022) is pending adjudication before my learned brother Shahid Waheed. J. this petition be also referred to the said learned Bench.

In view of above, office is directed to place this petition before the said learned Bench after soliciting orders from the Hon'ble Chief Justice."

15. **Writ Petition No. 4345/2022 filed by M/s Davis Pharmaceuticals Laboratories, Lahore [Mobil-K-75mg Tablet (Diclofenac Potassium: 75me) Reg. No. 041945 & Mobil-K l00mg Tablet (Diclofenac Potassium: l00mg) Reg. No. 063176]:**

Operative part of court order dated 25-01-2022 is reproduced as under:

"Subject to notice in the meanwhile proceedings under the impugned show cause notice dated 29th of December, 2021 shall continue but the final decision shall not be made till the next date of hearing"

16. **Writ Petition No. 23797/2022 filed by M/s Sapient Pharma, Lahore [Zainex 75mg Tablets (Diclofenac Potassium: 75mg) Reg. No. 069281]:**

Operative part of court order dated 19-04-2022 is reproduced as under:

"Since interim relief has already been granted in connected petition, subject to notice and in the meanwhile proceedings under the impugned show cause notice dated 06.04.2022 shall continue but the final decision shall not be made till the next date of hearing"

17. **Writ Petition No. 25530/2022 filed by M/s Pakheim International Pharma (Pvt) Ltd., Lahore [Fen-K SR Tablet 100mg (Diclofenac Potassium: 100mg) Reg. No. 023973]:**

18. **Writ Petition No. 23797/2022 filed by M/s Paramount Pharmaceuticals, Islamabad [Ronset SR Tablet 100mg (Diclofenac Potassium: 100mg) Reg. No. 052727]:**

Operative part of court order dated 21-04-2022 is reproduced as under:

"Subject to notice, in the meanwhile proceedings under the impugned show cause notice shall continue but the final decision shall not be made till the next date of hearing"

All the firms have challenged the Show Cause Notices issued for cancellation of their drugs stating violation of the decision taken in 70th Meeting of the DRAP Authority held on the 05-09-2019.

However, the decision taken in 70th Meeting of the DRAP Authority, has been reviewed in the 128th Meeting held on 14-12-2021, whereby Registration Board was allowed to review and dispose of registration of drugs keeping in view their safety and efficacy.

19. **Writ Petition No. 9832 of 2022 filed by Quaper Pvt. Ltd. Vs. FoP and others.**

In instant case, the Petitioner has challenged the decision taken by the Registration Board of the Drug Regulatory Authority of Pakistan in its 313th Meeting held on the 16th, 17th and 18th November, 2021, whereby the Petitioner has not been allowed to resume manufacturing of a drug by the name of 'Kaymax Tablets' *(as its registration had been suspended after its declaration as sub-standard by the Drugs Testing Laboratory)* till the determination of its safety and efficacy in accordance with the applicable law. Next date of hearing is 25-04-2022.

20. ***Decision of M-315 held on 01st Feb, 2022:***

Registration Board noted the information and advised to provide the opportunity of personal hearing in the next meeting of Registration Board.

21. While planning for 317th meeting of Registration Board, Division of PE&R has once again gone through a process of reviewing Diclofenac Potassium 75mg & 100mg Tablets based on all available facts and findings which have been summarized as under:

i. Diclofenac potassium is approved by various reference regulatory authorities in 12.5mg, 25mg and 50mg tablet strengths. As per the review of databases of all reference regulatory authorities (RRAs) approved by the Registration Board in its 275th meeting, it was observed that the maximum strength of diclofenac potassium in any dosage form is 50mg.

ii. However, in Pakistan diclofenac potassium 75 and 100mg are also available. Since DRAP is in process of reviewing the rationale, safety and efficacy of various approved formulations, therefore the formulation of diclofenac potassium 75 and 100mg tablets were also reviewed.

iii. Product monographs and SmPC of innovator's and generic versions of Diclofenac Potassium tablets approved by various RRAs have been reviewed, which depicts that the daily dose of diclofenac potassium is from 75-200mg in divided doses, whereas the maximum strength of available diclofenac potassium tablet is 50mg. Detailed recommendations regarding dosage as extracted from official websites of various RRAs have been reproduced as under:

S/N	RRA/ Product Detail	Recommended Dosage
1.	**USFDA**/ Cataflam 50mg Tablet	**Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.** • For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg three times a day. With experience, physicians may find that in some patients an initial dose of 100 mg of CATAFLAM, followed by 50 mg doses, will provide better relief. • For the relief of osteoarthritis, the recommended dosage is 100-150 mg/day in divided doses, 50 mg twice a day or three times a day. • For the relief of rheumatoid arthritis, the recommended dosage is 150-200 mg/day in divided doses, 50 mg three times a day or four times a day. • Furthermore, USFDA under the heading of 'warning' states as under: *"Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.* ***Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation.*** *Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.* ***No information is available from controlled clinical studies regarding the use of CATAFLAM in patients with advanced renal disease.*** *The renal effects of CATAFLAM may hasten the progression of renal dysfunction in patients with pre-existing renal disease (USFDA)."*
2.	**MHRA**/ Diclofenac Potassium 50mg	**Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.** • The recommended daily dose is 100-150mg in two or three divided doses. For milder cases, 75-100mg daily in two or three divided doses is usually sufficient. • In migraine an initial dose of 50mg should be taken at the first signs of an impending attack. In cases where relief 2 hours after

		the first dose is not sufficient, a further dose of 50mg may be taken. If needed, further doses of 50mg may be taken at intervals of 4-6 hours, not exceeding a total dose of 200mg per day.
3.	**TGA/** Voltaren Rapid 50mg Tablet	**After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.** • <u>Acute pain states with an inflammatory component:</u> As a rule, the initial daily dosage for adults is 100 to 150 mg. In milder cases, as well as for children over 14 years of age, 75 to 100 mg daily is usually sufficient. The total daily dosage should generally be prescribed in 2 or 3 fractional doses. Treatment is to continue for a maximum of 7 days. If the pain has not resolved satisfactorily after 7 days' treatment, the patient should be instructed to return for review by the doctor. • <u>Acute migraine</u> In migraine, an initial dose of 50 mg should be taken at the first signs of an impending attack. If the pain is not relieved within 2 hours of this initial dose, a further dose of 50 mg may be taken. If needed, further doses of 50 mg may be taken at intervals of 4-6 hours. The total dose to treat an acute migraine should not exceed 200 mg. The total daily dose should not exceed 200 mg. Diclofenac potassium should not be used for migraine prophylaxis. • <u>Symptomatic treatment of primary dysmenorrhoea</u> In primary dysmenorrhoea, initially a dose of 50 or 100 mg should be given followed by 50 mg three times daily for 3 days. Treatment should be started upon appearance of the first symptoms and, depending on their duration and severity, continued for up to three days. If the pain has not resolved satisfactorily after 3 days' treatment, the patient should be instructed to return for review by the doctor.
4.	**Health Canada/** Pms-Diclofenac K	**As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.** • The recommended daily dose for pms-DICLOFENAC K is one 50 mg tablet, every 6-8 hours as required for a total daily maximum amount of 100 mg. • For primary dysmenorrhea, treatment may be initiated on the first day with a loading dose of 100 mg, followed by 50 mg every six to eight hours after the initial dose if needed, for a maximum dose of 200 mg only on the first day. • Patients should be maintained on the lowest effective dose.
5.	**Swedish Medical Products Agency/** Voltaren T 50 mg Tablet	**Voltaren T treatment should be initiated at the lowest presumed effective dose, in order to be able to adjusted for therapy responses and possible side effects.** **Side effects can be minimized by using the lowest effective dose for the shortest possible duration of treatment that is necessary to control symptoms. In long-term treatment, a low dose is sought.** <u>For Adults:</u> • 50 mg up to 3 times per day. The maximum recommended daily dose is 150 mg.

		• In migraines, 50 mg is initially given at the first sign of a seizure. If relief is not achieved within the 2 hours, given an additional 50 mg. This can be repeated at intervals of 4-6 hours, with a maximum 150 mg per day.
6.	**BNF**/ Voltarol Rapid 50mg Tablet	• <u>Pain and inflammation in rheumatic disease and other musculoskeletal disorders</u> Adult: 75–150 mg daily in 2–3 divided doses • <u>Acute gout</u> Adult: 75–150 mg daily in 2–3 divided doses • <u>Postoperative pain</u> Adult: 75–150 mg daily in 2–3 divided doses • <u>Migraine</u> Adult: 50 mg, to be given at onset of migraine, then 50 mg after 2 hours if required, then 50 mg after 4–6 hours; maximum 200 mg per day.

iv. Keeping in view the above-mentioned information, it can be concluded that maximum daily dose range of Diclofenac Potassium is categorically described in available literature. However, 2-3 divided/fractional doses are recommended for administration which raise question regarding calculation of maximum single dose. In other words, clarity is required whether Diclofenac Potassium in strengths higher than 50mg can be administered as a single dose.

v. It is also pertinent to mention that **"use of lowest effective dose for the shortest duration"** has been emphasized. Furthermore, even for indications where 100mg is recommended, the same is mentioned as either initial dose or loading dose, requirement of which may be fulfilled by taking two tablets of 50mg.

22. Based upon the above review, following two questions were framed and were communicated for guidance to various RRA's including USFDA, Health Canada, MHRA UK, Sweden, TGA Australia and BNF.

a. Whether diclofenac potassium 75mg or 100mg tablet can be administered twice a day to achieve a maximum daily dose of 150 – 200mg

b. Any relevant clinical data which shows that administration of a single dose of 75 or 100mg diclofenac potassium is safe.

23. Response received from various RRAs is presented as under:

RRA	**Correspondent Name/ Designation/ e-mail**	**Contact Detail**	**Date of response**
USFDA	• Tisha Washington • International Program|Strategic Initiatives|OCD • Center for Drug Evaluation and Research • CDERINTLEXEC@fda.hhs.gov	U.S. Food and Drug Administration Tel: 301-796-1019 Tisha.Washington@fda.hhs.gov	24-02-2022
• According to the Orange Book, diclofenac potassium is available in 25mg and 50mg tablets only, whereas diclofenac sodium is also available in 75mg and 100mg delayed release and extended release tablets. • To provide you with insight on the dosing and dose limitation, the dosing information for Diclofenac sodium enteric-coated tablets of 25 mg, 50 mg, and 75 mg can be found below: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019201s035lbl.pdf • And for Diclofenac potassium immediate-release tablets of 50 mg below https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020142s021s022lbl.pdf • *The relevant page of the label of Diclofenac potassium immediate-release tablets of 50 mg is placed below:*			

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of Cataflam® (diclofenac potassium immediate-release tablets) and other treatment options before deciding to use Cataflam. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

After observing the response to initial therapy with Cataflam, the dose and frequency should be adjusted to suit an individual patient's needs.

For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg t.i.d. With experience, physicians may find that in some patients an initial dose of 100 mg of Cataflam, followed by 50-mg doses, will provide better relief.

For the relief of osteoarthritis the recommended dosage is 100-150 mg/day in divided doses, 50 mg b.i.d. or t.i.d.

For the relief of rheumatoid arthritis the recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d.

Different formulations of diclofenac [Voltaren® (diclofenac sodium enteric-coated tablets); Voltaren®-XR (diclofenac sodium extended-release tablets); Cataflam® (diclofenac potassium immediate-release tablets)] are not necessarily bioequivalent even if the milligram strength is the same.

HOW SUPPLIED

Cataflam® (diclofenac potassium immediate-release tablets)

50 mg – light brown, round, biconvex, sugar-coated tablets (imprinted Cataflam on one side and 50 on the other side in black ink)

Bottles of 100……..……..……..……..NDC 0078-0436-05

Do not store above 30°C (86°F). *Dispense in tight container (USP).*

RRA	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response
Swedish Medical Products Agency	• Ingrid Landberg • Head of department Efficacy and Safety 1 • ingrid.landberg@lakemedelsverket.se	P.O.Box 26, SE-751 03 Uppsala, Sweden Visiting address: Dag Hammarskjölds väg 42 Phone: +46 (0)18-17 46 00, Direct: +46 (0)18 174272 ingrid.landberg@lakemedelsverket.se www.lakemedelsverket.se	28-02-2022

- In Sweden the maximum diclofenac potassium dosage is in general 150 mg per 24 hours, and the recommended dosage is depending on the indication.
- This dosage can in general be divided into several doses.
- Unfortunately, we cannot provide any further data or support to address the two questions asked in your email, since these questions must be answered by the respective MAH for the respective medical product.
- Several issues needs to be considered for each case, for example diclofenac formulation, indication and patient population.

RRA	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response
Health Canada	bcansenquiries@hc-sc.gc.ca	Bureau of Cardiology, Allergy and Neurological Sciences BCANS Enquiries / Government of Canada bcans.enquiries@hc-sc.gc.ca	10-03-2022

		Bureau de cardiologie, allergologie et sciences neurologiques Enquêtes BCASN / Gouvernement du Canada bcans.enquiries@hc-sc.gc.ca	

- The Therapeutic Products Directorate (TPD) is the Canadian federal authority that regulates pharmaceutical drugs for human use. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations.
- Health Canada has not authorized a 75 mg or 100 mg tablet of diclofenac potassium. Only the 50 mg diclofenac potassium tablet is available.
- Generally speaking the recommended daily dose is one 50 mg tablet, every 6-8 hours as required for a total daily maximum amount of 100 mg.
- For primary dysmenorrhea, treatment may be initiated on the first day with a loading dose of 100 mg, followed by 50 mg every six to eight hours after the initial dose if needed, for a maximum dose of 200 mg only on the first day.
- Patients should be maintained on the lowest effective dose.
- More detailed information is available for diclofenac potassium products through the Health Canada's Drug Product Database.
- A 50mg powder/sachet formulation of diclofenac potassium is also available, CAMBIA® (diclofenac potassium). CAMBIA® (diclofenac potassium) is indicated for the acute treatment of migraine attacks with or without aura in adults 18 years and older. The maximum recommended daily dose is one sachet (50 mg).
- Health Canada is committed to transparency, and maintains many publicly available sources of information which you may find useful:
  - **The Drug Product Database:** https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
  - **The Drug Product Register:** https://hpr-rps.hres.ca/ for Summary Basis of Decision reports
  - **The Public Release of Clinical Information portal:** https://clinical-information.canada.ca/search/ci-rc
- As Health Canada has not authorized a 75 mg or 100 mg tablet of diclofenac potassium, we therefore suggest that to receive the information you are requesting, you contact manufacturers of these products directly, especially those with marketing authorizations in your country.

RRA	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response
UK MHRA **(**Medicines and Healthcare products Regulatory Agency)	• **Annabelle** • **MHRA Customer Experience Centre** • Communications and engagement team • Medicines and Healthcare products Regulatory Agency • RIS.NA@mhra.gov.uk	10 South Colonnade, Canary Wharf, London E14 4PU Telephone 020 3080 6000 gov.uk/mhra	22-03-2022

- In the UK, the recommended maximum daily dose of diclofenac is 150 mg.
- The maximum approved strength of diclofenac potassium in the UK is 50 mg as an immediate release tablet formulation.
- We have no data to support the efficacy or safety of 75 mg or 100 mg strength diclofenac potassium tablets.
- We have approved some products containing 75 mg or 100 mg of diclofenac but as oral modified release formulations. These contain alternative diclofenac salts e.g. diclofenac sodium.

RRA	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response

TGA Australia **(**Therapeutic Goods Administration)	• Liam • **TGA Contact Centre** Regulatory Assistance Section Regulatory Engagement Branch • info@tga.gov.au	Phone: 1800 020 653 Fax: 02 6203 1605 Email: info@tga.gov.au Therapeutic Goods Administration Department of Health PO Box 100 Woden ACT 2606 www.tga.gov.au	07-04-2022

- *Whether diclofenac potassium 75mg or 100mg tablet can be administered twice a day to achieve a maximum daily dose of 150 – 200mg*
  In Australia, this product is only registered as a 25mg or 50mg product, so cannot directly comment on this query. The repository of PIs is available https://www.tga.gov.au/picmi-search-facility

- *Any relevant clinical data which shows that administration of a single dose of 75 or 100mg diclofenac potassium is safe.*
  Noting the response to the above, the Product Information would be the source of truth in terms of recommended dosing. The TGA cannot provide any data that was submitted by Australian sponsors for the purpose of evaluations to other parties, including overseas regulators without the sponsor's express permission.
- We would suggest contacting the Australian sponsors directly if they would be willing to share any data that would assist.

24. In line with the decision of 315th meeting of Registration Board, following registration holders were issued show cause & personal hearing notices stating:

"Diclofenac Potassium in strengths higher than 50mg have not been approved by any of the reference regulatory authorities (RRAs) adopted by the Registration Board in its 275th meeting and the safety & efficacy in strengths higher than 50mg are not established by any RRA. The above information provokes the provisions of Section 7 (l l)(d) and 42 of the Drugs Act, 1976. Accordingly, registration holders are required to show cause as to why the registration of their products may not be cancelled with immediate effect."

Diclofenac Potassium **Date & Time of Hearing: 16th May, 2022 at 10:00A.M.**			
Sr. No.	**Reg No**	**Brand Name & composition**	**Registration Holder**
1.	64588	Daikin Tablets 75mg Diclofenac Potassium ... 75mg	3S Pharmaceuticals (Pvt) Ltd., 5-Km, Off Raiwind Manga Road, Lahore. , Lahore
2.	58146	Zulfenec –P 75mg Tablet Diclofenac Potassium……..75 mg	M/s Adamjee Pharmaceuticals (Pvt.) Ltd., Plot 39, Sector 15, Korangi Industrial Area, Karachi.
3.	58147	Zulfenec –P 100mg Tablet Diclofenac Potassium….100 mg	M/s Adamjee Pharmaceuticals (Pvt.) Ltd., Plot 39, Sector 15, Korangi Industrial Area, Karachi.
4.	76892	Dicgesic-K Tablets 75 mg Diclofenac Potassium: 75mg	M/s. Alen Pharmaceuticals (Pvt) Ltd., 138 Nowshera Industrial Estate, Risalpur.
5.	57517	Lyon Tablet Diclofenac Potassium ... 75mg	Alfalah Pharma (Pvt) Ltd., 12-Km, Sheikhupura Road, Lahore. , Lahore

6.	50330	Kemipan Plus Tablet Diclofenac Potassium……75mg	M/s. Alkemy Pharmaceutical Laboratories (Pvt) Ltd, Hyderabad, P-9 SITE, Hyderabad.
7.	54702	D-Fine P 75mg Tab Diclofenac Potassium ……75mg	M/s Alliance Pharmaceuticals (Pvt) Ltd, Plot # 112-A, Hayatabad, Industrial Estate, Peshawar.
8.	52438	Xion Tablets 75mg Diclofenac Potassium ... 75mg	Allmed (Pvt) Ltd., Plot No. 590 Sundar Industrial Estate Lahore. , Lahore
9.	36326	Aldal Tablets Diclofenac Potassium…75mg	M/s. Alson Pharmaceuticals, 169, Road No.7-B, Industrial Estate Hayatabad, Peshawar.
10.	37849	Phenpal Capsule Each capsule contains:- Diclofenac Potassium 75mg	M/s. Alson Pharmaceuticals, 169, Road No.7-B, Industrial Estate, Hayatabad, Peshawar.
11.	57784	Demsum 75 mg Tablet Diclofenac Potasium……75mg	Amarant Pharamceuticals (Pvt) Ltd., 158-D Den Toro Gadap Road Super Highway Karachi., Karachi Previous Title: Lexicon Pharmaceuticals Pvt. Ltd. Karachi
12.	54527	Ariflam 75mg Capsule Diclofenac Potassium enteric coated pellets equivalent to ….75mg	M/s. Aries Pharmaceuticals (Pvt) Ltd, 1-W, Industrial Estate, Hayatabad, Peshawar.
13.	60292	Ariflam 100mg SR Capsule Diclofenac Potassium enteric coated pellets equivalent to Diclofenac Potassium….100mg	M/s. Aries Pharmaceuticals (Pvt) Ltd, 1-W, Industrial Estate,Hayatabad, Peshawar.
14.	74198	Peflam Tab Diclofenac Potassium ... 75mg	Arsons Pharmaceutical Industries (Pvt) Ltd., 22-Km Multan Road Off 2.5-KM Defence Road, Lahore., Lahore
15.	59625	Nostif-K Tablet Diclofenac Potassium ... 75mg	Axis Pharmaceuticals , 3-B Value Addition City 1.5 Km Khurrianwala – Sahanwala Road Faisalabad., Faisalabad
16.	30959	Artimov-K Tablets 75mg Diclofenac Potassium …..75mg	M/s Barrett Hodgson Pakistan (Pvt) Ltd. F/423, S.I.T.E., Karachi.
17.	30960	Artimov-K Tablets 100mg Diclofenac Potassium …..100mg	M/s Barrett Hodgson Pakistan (Pvt) Ltd. F/423, S.I.T.E., Karachi.
18.	77028	Basocap -75mg Capsule Diclofenac Potassium ... 75mg	Basel Pharmaceuticals, 227-Phase-II Multan Industrial Estate Multan, Multan
19.	31128	Beflam Tablets 75mg Diclofenac Potassium ... 75mg	Batala Pharmaceuticals, 23/B Small Industrial Estate No. 2 Near Wapda Town, Khiali Bypass Gujranwala, Gujranwala
20.	21577	Keygesic Tablet 75mg Diclofenac Potassium ... 75mg	Benson Pharmaceuticals, Plot No.119 Street No.8, I-10/3 Industrial Area Islamabad. , Islamabad
21.	62591	Diclotal K Tablet 75mg Diclofenac Potassium ... 75mg	Berlex Lab. International, 10-Km Nangshah Chowk Karachi Road Multan, Multan

22.	38342	Osti-P Tablet Diclofenac Potassium ... 75mg	Bio Fine Pharmaceuticals (Pvt) Ltd., 74 Industrial Estate Multan., Multan
23.	65195	Biodic-P Diclofenac Potassium ... 75mg	Biorex Pharmaceuticals, Plot No.292 Industrial Triangle Kahuta Road Islamabad., Islamabad
24.	74501	Caldic 75mg Tablet Diclofenac Potassium….75mg	M/s Caliph Pharmaceuticals (Pvt) Ltd, Plot No. 17 Industrial Estate, Risalpur, Khyber Pakhtunkhwa.
25.	24333	Kalfen Tablet 75mg Diclofenac Potassium ... 75mg	Candid Pharmaceuticals, Opp Pasrur Sugar Mills Sialkot Road, Pasrur., Pasrur
26.	50019	Carafenac-P Tablets 75mg Diclofenac Potassium ... 75mg	Caraway Pharmaceuticals, Plot No. 12 Street No. N-3 National Industrial Zone (RCCI) Rawat Islamabad., Islamabad
27.	54325	Fapa 100mg SR Tablet Diclofenac Potassium ... 75mg	Caylex Pharmaceuticals (Pvt) Ltd., 27-Km Mian Raiwind Road Lahore., Lahore
28.	48383	Deflam Tablet 75mg Diclofenac Potassium ... 75mg	CCL Pharmaceuticals (Pvt) Ltd., 62 Industrial Estate Kot Lakhpat Lahore, Lahore
29.	36727	Confenac-K Tablets Diclofenac Potassium…….75mg	M/s. Convell Laboratories, Saidu Sharif, Swat.
30.	37887	Diclovel Tablets Diclofenac Potassium…..75mg	M/s. Convell Laboratories, Saidu Sharif, Swat.
31.	66480	Frisky Tablet Diclofenac Potassium ... 75mg	Crest Pharmaceuticals, Plot No. 43 Industrial Triangle Kahuta Road Islamabad., Islamabad
32.	56377	Dlf-K Diclofenac Potassium ... 75mg	Crown Pharmaceuticals, 286 Kahuta Industrial Triangle Islamabad., Islamabad
33.	41945	Mobil K 75mg Tablet Diclofenac Potassium ... 75mg	Davis Pharmaceutical Laboratories , Plot No. 121 Industrial Triangle Kahuta Road Islamabad., Islamabad
34.	63176	Mobil-K 100mg Tablets Diclofenac Potassium ...100mg	Davis Pharmaceutical Laboratories , Plot No. 121 Industrial Triangle Kahuta Road Islamabad., Islamabad
35.	32102	Dicfin 75mg Tablets Each tablet contains:- Diclofenac Potassium 75mg	M/s Dr. Raza Pharma, Plot No. 44-C, Industrial Estate, Hayatabad, Peshawar.
36.	51172	Engrol 75mg Capsules Diclofenac Potassium ... 75mg	English Pharmaceutical Industries, Indus Link Katarband Road Thokar Niaz Beg, Multan Road Lahore., Lahore
37.	23811	Ardi-K Tablets Diclofenac Potassium ... 75mg	English Pharmaceutical Industries, Indus Link Katarband Road Thokar Niaz Beg, Multan Road Lahore., Lahore

38.	46215	Brisc 75mg Tablet Diclofenac Potassium ... 75mg	Envoy Pharmaceuticals (Pvt) Ltd., 27-Km Multan Road Maraka Lahore , Lahore
39.	58420	Eplopot Tablet Diclofenac Potassium …..75 mg	M/s E-Pharm Laboratories, A-40, S.I.T.E. Super Highway Industrial Area North, Karachi.
40.	56720	Dilo-K 75mg Capsule Diclofenac Potassium75mg	M/s Farm Aid Group, Plot # 3/2, Phase I & II, Hattar Industrial Estate, Haripur.
41.	60923	Flexura 75mg Tablet Diclofenac Potassium…….75mg	M/s. Fassgen Pharmaceuticals, Plot No. 67/1-A, Phase-III, Industrial Estate, Hattar.
42.	38169	Synoflam- 75Mg Tablets Diclofenac PotassiumUSP…..75mg	M/s Fedro Pharmaceutical Labs (Pvt) Ltd., 149-Industrial Estate, Jamrud Road, Hayatabad.
43.	49839	D-K Tablet 75mg Diclofenac Potassium ... 75mg	Ferroza International Pharmaceuticals (Pvt) Ltd., 33-Km Ferozepur Road Lahore., Lahore
44.	46893	Feflam-75 Tablets Diclofenac Potassium ... 75mg	Festal Laboratories, Jinnah Industries Link Kattar Band Road Thokar Niaz Baig Lahore., Lahore
45.	36772	Pofen 75Mg Tablets Diclofenac Potassium……..75mg	M/s Fozan Pharmaceutical Industrial (Pvt) Ltd.,36- A, Industrial Estate, Hayatabad, Peshawar.
46.	54195	Frendic-P Tablet 75mg Diclofenac Potassium ... 75mg	Friends Pharma (Pvt) Ltd., 31-Km Ferozepur Road Lahore., Lahore
47.	49013	Caveron Tab 75mg Diclofenac Potassium ... 75mg	FYNK Pharmaceuticals, 19-Km Ferozepur Road G.T. Road Kala shah Kaku Lahore. , Lahore
48.	46175	Reform Capsules 75mg. Diclofenac Potassium…….75mg	M/s Genome Pharmaceuticals (Pvt.) Ltd. Plot # 16/I-Phase IV, Industrial Estate, Hattar, Haripur Previous Title: Silver Oak Corporation, Plot No.16/1-Phase IV, Industrial Estate, Hattar
49.	63038	Arthopot Capsule Diclofenac Potassium…..75mg	M/s. Gillman Pharmaceuticals, 14/2-A. Phase I & II, Industrial Estate,Hattar.
50.	38553	Glift-K 75mg Tablet Diclofenac Potassium ... 75mg	Glitz Pharma, Plot No 265 Industrial Triangle Kahuta Road Islamadad. , Islamabad
51.	54918	Artinil-K SR 100mg Tab Diclofenac Potassium ...100mg	Global Pharmaceuticals, Plot No 204-205 Kahuta Triangle Industrial Area Islamabad., Islamabad
52.	21634	Artinil-K 75mg Tab Diclofenac Potassium ... 75mg	Global Pharmaceuticals, Plot No 204-205 Kahuta Triangle Industrial Area Islamabad., Islamabad
53.	56183	Potafin Diclofenac Potassium ... 75mg	Goodman Laboratories, Plot No.5 St: No. S-5 National Industrial Zone Rawat Islamabad., Islamabad
54.	54273	Muskel 75mg Tablets Diclofenac Potassium ... 75mg	Hamaz Pharmaceuticals (Pvt) Ltd., 13-Km Lutafabad Bosan Road Multan. , Multan

55.	59883	Zofen-K Tablets 75mg Each tablet contains:- Diclofenac Potassium … 75mg	Harmann Pharmaceutical Laboratories (Pvt) Ltd., 16-Km Multan Road Lahore. , Lahore
56.	50107	Diclokam-K Tablets 75mg Diclofenac Potassium ... 75mg	Harrison Pharmaceuticals, 10-Km Lahore Road Sargodha. , Sargodha
57.	60366	Harrifan-K 100mg Tablet Diclofenac Potassium ...100mg	Harrison Pharmaceuticals, 10-Km Lahore Road Sargodha. , Sargodha
58.	68362	Rxoflam Tablets 75mg. Diclofenac Potassium……75mg	M/s. Healer Laboratories (Pvt) Ltd., 96/102-C SIE Kohat Road, Peshawar.
59.	41483	Getab tablet Diclofenic Potassium…… 75mg	M/s Hicon Pharmaceuticals. 131-Industrial Estate, Hayatabad, Peshawar.
60.	55997	Qufen -K 75mg Tablet Diclofenac Potassium……..….75mg	M/s High-Q Pharmaceuticals, Plot No.224, Sector 23, Korangi Industrial Area, Karachi.
61.	22543	Maxit 75 mg Tablet Diclofenac potassium… 75 mg	M/s Hilton Pharma (Pvt.) limited, Plot # 13-14, Sector 15, Korangi Industrial Area, Karachi.
62.	62476	Kaynac Capsule 75mg Diclofenac Potassium ... 75mg	Hoover Pharmaceuticals (Pvt) Ltd., Plot No.16 Zain Park Industrial Area Saggain By Pass Road Lahore., Lahore
63.	31800	Ketagesic-75 Tablet Diclofenac Potassium ... 75mg	Hygeia Pharmaceuticals, Plot No. 295 Industrial Triangle Kahuta Road Islamabad. , Islamabad
64.	69285	Denum K Tablets Diclofenac Potassium ... 75mg	Irza Pharma (Pvt) Ltd., 10.2-Km Lahore Sheikhupura Road P.O Kot Abdul Malik District Sheikhupura., Sheikhupura
For product at S.No.65, M/s Leads Pharma Pvt. Ltd., Islamabad has already been issued letter (dated 03-09-2021) regarding "Cancellation of Registration of Drugs" registered under Tablet (General) Section consequent to the "Withdrawal/ Voluntary Surrender of Licensed Sections (including Tablet General section) by the Firm" i.e., communicated vide Licensing Division's letter dated 15-01-2021.			
65.	50953	Diclosoft- K Tablets 75mg Diclofenac Potassium ... 75mg	Leads Pharma (Pvt) Ltd., Plot No. 81-A Street No. 6 I-10/3 Islamabad., Islamabad
66.	74597	Nexfen Tablets 75 mg. Diclofenac Potassium……75 mg	M/s. Libra (Pvt) Ltd, 77-Peshawar Industrial Estate, Hayatabad, Peshawar.
67.	65234	Linofenac-P 75mg Tablet Diclofenac Potassium ... 75mg	Linear Pharma, Plot No. 18 S. No. S-4 National Industrial Zone (RCCI) Rawat Islamabad., Islamabad
68.	63262	Diclotus-K Diclofenac Potassium ... 75mg	Lotus Pharmaceutials (Pvt) Ltd. , Plot No.118-A Street No. 8, I-10/3 Industrial Area Islamabad. , Islamabad
69.	39198	Catafen 100 Tablets Diclofenac Potassium.100mg	M/s Macter International Limited. F-216, S.I.T.E, Karachi.
70.	38450	Kaldic Diclofenac Potassium ...100mg	Mass Pharma (Pvt) Ltd., 17 Km Ferozpur Road Lahore., Lahore
71.	28866	Inflaban-75 Tablet Diclofenac Potassium ... 75mg	Medera Pharmaceuticals (Pvt) Ltd., 249-A Industrial Triangle Kahuta Road Islamabad., Islamabad

72.	53260	Defenac 100mg Tablet Diclofenac Potassium :100mg	M/s Mediate Pharmaceuticals (Pvt) Limited, Plot 150-151, Sector 24, Korangi Industrial Area, Karachi.
73.	73586	Defenac 75mg Capsule Diclofenac Potassium: 75mg	M/s Mediate Pharmaceuticals (Pvt) Limited, Plot 150-151, Sector 24, Korangi Industrial Area, Karachi.
74.	61574	Dicsod-K Tablet Each tablet contains:- Diclofenac potassium … 75 mg	M/s Medicaids (Pvt) Limited, Plot No. 10, Sector-27, Korangi Industrial Area, Karachi.
75.	31178	Mediflam SR 100mg Tablets Diclofenac Potassium ... 75mg	Mediceena Pharma (Pvt) Ltd., 27 Km Raiwind Road Lahore, Lahore
76.	73273	Anti-Pain 100mg Capsules Diclofenac Potassium Pellets eq. to Diclofenac Potassium: 100mg	M/s. Medicraft Pharmaceuticals (Pvt.) Ltd., 126-B Industrial Estate Hayatabad, Peshawar.
77.	64022	Anti-Pain 75mg Capsule Diclofenac Potassium Pellets equivalent to Diclofenac Potassium……..75mg	M/s. Medicraft Pharmaceuticals (Pvt.) Ltd., 126-B Industrial Estate Hayatabad, Peshawar.
78.	64026	DP-Med 100mg Tablet Diclofenac Potassium.…100mg	M/s. Medicraft Pharmaceuticals (Pvt.) Ltd., 126-B Industrial Estate Hayatabad, Peshawar.
79.	69004	Kenac Tablet 75mg Diclofenac Potassium ... 75mg	Medisave Pharmaceuticals, Plot No.578-579 Sundar Industrial Estate Lahore., Lahore
80.	73124	Kalium 75mg Tablet Diclofenac Potassium ... 75mg	Medisynth Pharmaceuticals, Plot No. 55 Street No. S-5 National Industrial Zone Rawat Islamabad., Islamabad
81.	68456	Volmed-K Capsule Diclofenac Potassium……75mg	M/s. Meditech Pharmaceuticals, 15-D Industrial Estate, Jamrud Road, Peshawar
82.	66670	Qrelif-75 Tablets Diclofenac Potassium ... 75mg	Medizan Laboratories (Pvt) Ltd., Plot No 313 Industrial Triangle Kahuta Road Islamabad., Islamabad
83.	59535	D-Fenac Tablets Diclofenac Potassium ... 75mg	Medley Pharmaceuticals, 41/A Punjab Small Industries Estate Jhang Bahtar Road Wah Cantt., Wah Cantonment
84.	43655	Marinac-P 75 tablet Diclofenac Potassium ... 75mg	Miracle Pharmaceuticals (Pvt) Ltd., Plot No-8 Street No-5 National Industrial Zone Rawat, Islamabad, Islamabad
85.	62636	Diclofil P Tablet Diclofenac Potassium ... 75mg	Murfy Pharmaceuticals (Pvt) Ltd., 8-Km Raiwind Road Lahore., Lahore
86.	43908	Digam Tablets 75mg Diclofenac Potassium: 75mg	M/s. Navegal Laboratories, Plot No. 41/1-A-2,Phase-I Industrial Estate Hattar, Haripur.
87.	68239	Naveflam Capsules 75mg. Diclofenac Potassium….75mg	M/s. Navegal Laboratories, Plot No. 41/1-A-2,Phase-I Industrial Estate Hattar, Haripur.
88.	38016	Dicloned-k 75mg tablet Diclofenac Potassium USP…..75mg	M/s Nenza Pharmaceuticals Pvt Ltd 33-A, Industrial Estate Hayatabad, Peshawar

89.	42984	Movom-P Capsules 75mg Diclofenac Potassium (enteric coated granules): 75mg	M/s Nenza Pharmaceuticals Pvt Ltd 33-A, Industrial Estate Hayatabad, Peshawar
90.	42985	Movom-P Capsules 100mg Diclofenac Potassium (enteric coated granules): 100mg	M/s Nenza Pharmaceuticals Pvt Ltd 33-A, Industrial Estate Hayatabad, Peshawar
91.	43982	Neofenik-75 Tablets Diclofenac Potassium ... 75mg	M/s Neomedix Plot No. 5/N-5 National Industrial Zone, Rawat Islamabad.
92.	39800	Noafilm Tablet 100mg Diclofenac Potassium…...100mg (Anti-rheumaticsystemic)	M/s Noa Hemis Pharmaceuticals, Plot #154, Sector 23, Korangi Industrial Area, Karachi.
93.	42123	Noafilm-75 Tablet 75mg Diclofenac Potassium……75mg (Anti-rheumaticsystemic)	M/s Noa Hemis Pharmaceuticals, Plot #154, Sector 23, Korangi Industrial Area, Karachi.
94.	43605	Declam Tablets 75mg Diclofenac Potassium ... 75mg	NovaMed Pharmaceuticals (Pvt) Ltd., 28-Km Ferozepur Road Lahore, Lahore
95.	64842	Declam Tablet 100mg Diclofenac Potassium ...100mg	NovaMed Pharmaceuticals (Pvt) Ltd., 28-Km Ferozepur Road Lahore, Lahore
96.	56250	Dipolive 75mg Tablet Diclofenac Potassium ... 75mg	Olive Laboratories, Plot No.52-S-6 National Industrial Zone Rawat Rawalpindi., Rawalpindi
97.	56977	Olitass Diclofenac Potassium ... 75mg	Olive Laboratories, Plot No.52-S-6 National Industrial Zone Rawat Rawalpindi., Rawalpindi
98.	23973	Fen-K SR Tablet 100mg Diclofenac Potassium ... 10mg	Pakheim International Pharma (Pvt) Ltd., 28 Km Ferozepur Road Lahore., Lahore
99.	52552	Tasilex Tablets 75mg Diclofenac Potassium ... 75mg	Panacea Pharmaceuticals, Plot No.4 Street No.S-6 National Industrial Zone Rawat Islamabad., Islamabad
100.	52803	Tasium Capsule 75mg Diclofenac Potassium ... 75mg	Panacea Pharmaceuticals, Plot No.4 Street No.S-6 National Industrial Zone Rawat Islamabad., Islamabad
101.	52727	Ronset SR Tablets Diclofenac Potassium ...100mg	Paramount Pharmaceuticals, 36 Industrial Triangle, Kahuta Road Islamabad., Islamabad
102.	38437	Phlodic-K Tablet Diclofenac Potassium ... 75mg	Pearl Pharmaceuticals, Plot No 204 Street No. 1 I-10/3 Industrial Area Islamabad., Islamabad
103.	32086	Tonek Tablet 75mg Diclofenac Potassium …75mg	M/s. Polyfine Chempharma, 51 Industrial Estate, Hayatabad, Peshawar.
104.	59971	Reuqin-75mg Tablet Diclofenac Potassium ... 75mg	Qintar Pharmaceuticals, 14-A Small Industrial Estate Lahore Road Sargodha., Sargodha
105.	46202	Kaymax Tablet Diclofenac Potassium ... 75mg	Quaper (Pvt) Ltd., 26-A S.I.E. Lahore Road Sargodha., Sargodha

106.	40187	Relsex 75mg Tablet Diclofenac Potassium ... 75mg	Rasco Pharma (Pvt) Ltd., 5.5 Km Raiwind Road Ali Razabad Lahore., Lahore
107.	58263	Velflex 100mg Tablet Diclofenac Potassium …100 mg	M/s Ray Pharma (Pvt) Ltd., S-58, S.I.T.E, Karachi.
108.	58262	Velflex 75 mg tablet Diclofenac Potassium ….75 mg	M/s Ray Pharma (Pvt) Ltd.,S-58, S.I.T.E Karachi.
109.	60445	Relic Tablet 75mg Diclofenac Potassium ... 75mg	M/s Raymond Pharmaceuticals Lahore (Formerly Home Chemical Industries), 16-KM Multan Road Lahore.
110.	66886	Regopyrin Tablet 75mg Diclofenac Potassium: 75mg	M/s. Regent Laboratories, C-20, S.I.T.E Super Highway, Karachi.
111.	65134	Ronac Tablets 75mg Diclofenac Potassium ... 75mg	Rogen Pharmaceuticals, Plot No. 30 S-4 National Industrial Zone Rawat Islamabad, Islamabad
112.	65135	Ronac SR Tablets 100mg Diclofenac Potassium ...100mg	Rogen Pharmaceuticals, Plot No. 30 S-4 National Industrial Zone Rawat Islamabad, Islamabad
113.	56701	Volden Fort K 75mg Tablet Diclofenac Potassium ... 75mg	Rotex Pharma (Pvt) Ltd., Plot No. 206-207 Industrial Triangle Khuta Road Islamabad, Islamabad
114.	62985	Diclosaf-P 75mg Tablets Diclofenac Potassium…..75mg	M/s. Saaaf Pharmaceutical Industries, Plot No. 15, Nowshera Industrial Estate, Risalpur.
115.	64198	Diclosaf-P SR 100mg Tablets Diclofenac Potassium…….100mg	M/s. Saaaf Pharmaceutical Industries, Plot No. 15, Nowshera Industrial Estate, Risalpur.
116.	55109	Dyfe-P 100mg SR Tablet Diclofenac Potassium…100mg	M/s Safe Pharmaceuticals (Pvt.) Ltd., Plot C-I-20, Sector 6-B, North Karachi Industrial Area, Karachi.
117.	55108	Dyfe-P 75mg Tablet Diclofenac Potassium…75mg	M/s Safe Pharmaceuticals (Pvt.) Ltd.,Plot C-I-20, Sector 6-B, North Karachi Industrial Area, Karachi.
118.	69281	Zainex 75mg Tablets Diclofenac Potassium ... 75mg	Sapient Pharma, 123-S Industrial Area Kot Lakhpat Lahore., Lahore
119.	36815	Dic-P 75Mg Tablets Diclofenic Potassium…….75mg	M/s Shaheen Pharmaceuticals. 3 km, Murghzar Road, Saidu Sharif, Swat.
120.	49385	Lofen 75mg Tablet Diclofenac Potassium ... 75mg	Shawan Pharmaceuticals, Plot No. 37 Road NS-1 National Industrial Zone Rawat Rawalpindi.
121.	64791	Pointer 75 Capsule Diclofenac Potassium ... 75mg	Shrooq Pharmaceuticals (Pvt) Ltd, 21-Km Ferozepur Road, Lahore., Lahore
122.	40304	Moven 75mg Tablet Diclofenac Potassium ... 75mg	Shrooq Pharmaceuticals (Pvt) Ltd, 21-Km Ferozepur Road, Lahore., Lahore
123.	72136	Siclo 75mg Tablet Diclofenac Potassium ... 75mg	Siam Pharmaceuticals, Plot No. 217 Industrial Triangle Kahuta Road Islamabad., Islamabad
124.	24049	Rheumatin-K Tablet 75mg Diclofenac Potassium ... 75mg	Siza International (Pvt) Ltd., 18-Km Main Ferozepur Road Lahore, Lahore

125.	57612	Detran-P 75mg Tablet Diclofenac Potassium ... 75mg	Sunshine Pharmaceuticals, Emanabad, G.T. Road, Gujranwala, Gujranwala
126.	60965	Diclowan-P 75mg Tablet Diclofenac Potassium ... 75mg	Swan Pharmaceutical (Pvt) Ltd., 11-E Industrial Triangle Kahuta Road Islamabad.
127.	23822	Klic-F 75mg tablet Diclofenac Potassium: 75mg	M/s Tabros Pharma (Pvt) limited, L-20/B, Sector-22, Federal B Industrial Area, Karachi.
128.	65546	Theradic-P Tablet 100mg Diclofenac Potassium ...100mg	Theramed Pharmaceuticals (Pvt) Ltd., 45-Km Multan Road Lahore., Lahore
129.	70233	Triclo-K 75mg Capsules Diclofenac Potassium ... 75mg	Trison Research Labortories (Pvt) Ltd., 27-A Punjab SIE Sargodha. , Sargodha
130.	52707	Unifin Tablet 75mg Diclofenac Potassium ... 75mg	Unison Chemical Works, 15 Km Raiwind Road Lahore., Lahore
131.	47294	Dic-P 100mg Tablets Diclofenac Potassium: 100mg	M/s Unitech Pharmaceuticals (Pvt) Ltd. Plot No. 4/116, Sector 21, Korangi Industrial Area, Karachi.
132.	27876	Signa 75mg Tablet Diclofenac Potassium ... 75mg	Valor Pharmaceuticals, 124/A Kahuta Triangle Industrial Area Islamabad. , Islamabad
133.	78831	VALRON-P 75 Tablets Diclofenac Potassium ... 75mg	Venus Pharma, 23 Km Multan Road Lahore. , Lahore
134.	37574	Diclovis-K 75Mg Tablets Diclofenac Potassium ... 75mg	Vision Pharmaceuticals, Plot No. 22-23 Industrial Triangle Kahuta Road Islamabad, Islamabad
135.	56845	Detaflam Tablet 75mg Diclofenac Potassium ... 75mg	Webros Pharmaceuticals, Plot No. 1 Street No. 10 National Industrial Zone Rawat Islamabad. , Islamabad
136.	65126	Relpain Diclofenac Potassium ... 75mg	Well & Well Pharma (Pvt) Ltd., Plot No.7 Street S-8 National Industrial Zone RCCI Rawat Islamabad., Islamabad
137.	68326	Dolwel 75mg Tablet Diclofenac Potassium……75mg	M/s Welmark Pharmaceuticals, Plot #122, Block B, Phase 5, Industrial State, Hattar.
138.	24273	Antiflam Tabelts Diclofenac Potassium ... 75mg	Wilshire Laboratories (Pvt) Ltd ., 124/1 Industial Estate Kot Lakhpat Lahore. , Lahore
139.	72983	Declowin 75mg Tablet Diclofenac Potassium ... 75mg	Winilton Pharmaceuticals (Pvt) Ltd., Plot No. 45 Street No. S-5 National Industrial Zone Rawat Rawalpindi., Rawalpindi
140.	47860	Achex Diclofenac Potassium ... 75mg	Wise Pharmaceuticals, Plot No. 3-A Street S-1 National Industrial Zone, Rawat Islamabad.

141.	56529	Pofac 75mg tablet Diclofenac Potassium……75mg	M/s. Wnsfeild Pharmaceuticals, Plot.No.122, Block-A, Phase-V,Industrial Estate Hattar, Haripur.
142.	57985	Painogin 75mg Tablet Diclofenac Potassium…...75mg	M/s Zanctok Pharmaceuticals Laboratories, F-5 S.I.T.E Area,Hyderabad.
143.	58404	Corom-P 75mg Tablet Diclofenac Potassium …..75 mg	M/s Zephyr Pharmatec (Pvt.) Ltd, A-39, SITE II, Super Highway, Karachi.
144.	35988	Quikrel 75mg Tablet Each tablet contains:- Diclofenac Potassium…..... 75mg	M/s. Z-Jans Pharmaceuticals (Pvt) Ltd., 148-A, Industrial Estate Hayatabad, Peshawar.
145.	054273	Muskel 75mg Tablet Each tablet contains:- Diclofenac Potassium…..... 75mg	Hamaz Pharmaceuticals (Pvt) Ltd., 13-Km Lutafabad Bosan Road Multan.
146.	057662	K-Lam 75mg Tablet Each tablet contains:- Diclofenac Potassium…..... 75mg	DrugPharm (Pvt) Ltd. 28-Km, Sheikhupura Road, Lahore

25. Furthermore, following responses have been received against the show cause notices:

S.NO	COMPANY NAME	RESPONSE
1.	**M/s Rotex Pharma Pvt Ltd, Islamabad**	In response to your letter No. F.5-6/2021 - Reg-11 (M-313) (Misc.) date 29/12/2021, we would like to inform you that the registration of the subject Product i.e. Volden Fort K 75mg Tablet may not be cancelled with immediate effect, because we have the following inventory in hand; **i. Finished Goods in warehouse 38,893 packs** **ii. Diclofenac Potassium (API) in inventory 308kg** **iii. Diclofenac Potassium (API) LC opened (See attached) 1000kg** Therefore, it is requested that we may please be allowed to consume above stock before cancellation of Registration.
2.	**M/s Alfalah Pharma (Pvt) Ltd, Lahore**	With reference to your letter no. F.5-6/2021-Reg-II(M-313)(Misc), dated 29-12-2021, we M/s Alfalah Pharma (Pvt.) Ltd., 12 Km Sheikhupura Road, Lahore, had received a show cause notice regarding the Cancellation of Registration of our product "LYON 75MG TABLET (Diclofenac potassium)" having registration no. 057517. We honor the board decision and it is so correct that there is no approved reference from any RRAs, but it is humbly requested in you honor that we have registered this product since dated 04-06-2009 (copy of registration letter is attached) and we are selling it on doctor's prescription. We have a huge market regarding its use. We had never any complaint from any doctor or patient regarding its use. We had done stability study of three different batches on both Accelerated (40°C 2°C and 75% + 5% RH) and Real time (30°C 2°C and 65% + 5% RH) at different intervals, the results of that are satisfactory (copy attached). Kindly allow us to continue quality production of "LYON 75MG TABLET (Diclofenac potassium)". Your decision is highly appreciated.
3.	**M/s Candid Pharma, Lahore**	Please refer your letter No.F.5-6/2021-Reg-II(M-313)(Misc) dated 29.12.2021 regarding the subject cited above. We, Candid Pharmaceuticals, hereby submit that any decision taken up by the Drug Registration Board in interest of general public

		regarding fate of Diclofenac potassium 75mg will be acceptable to us.
4.	**M/s Lotus Pahrmaceuticals (Pvt) Ltd, Islamabad**	With reference to your letter No F.5-6/2021-Reg-II (M-313) (Misc) dated 29th December 2021, it is stated that we are not manufacturing Diclofenac Potassium (Diclotus-K 75mg) since July-2021 Furthermore, we have no intention to manufacture above mentioned product in future.
5.	**M/s Adamjee Pharaceuticals Pvt Ltd**	We reference to your letter no. F-3-6/2021 Reg-1 (M313) Misc dated 7th January 2022, we have objection to cancellation of Zulfenac-P 75mg and Zulfenac-P 100mg tablet. We will utilize our raw material to manufacture Adafenac-P 50mg tablets (diclofenac Potassium 50mg Registration No. 58145.
6.	**M/s Novamed Pharmaceuticals Pvt Ltd**	With reference to your show cause notice No.F.5-6/2021-Reg-II(M-313)(Misc) dated 29-12-2021 and 07-01-2022 and personal hearing Notice No.F.3-2/2022-Reg-I (M-317)(Misc) dated 06-04-2022 on the subject cited above, we want to explain our narrative for our registered drug Declam Tablet 75mg (Diclofenac Potassium 75mg) and Declam Tablet 100mg (Diclofenac Potassium 100mg) having registration No.064842 & 043605. Declam Tablet 75mg and Declam Tablet 100mg, both the strength are registered with the DRAP since 13-06-2006 and 10-08-2010 respectively and are being marketed since registration. However, during this period of 12 years no adverse event has been reported till date. When there is a concern of efficacy and safety of drug, pharmacovigilance department of the competent authority is requested to conduct a risk based study associated with efficacy and safety pf questioned strengths of said drugs and accordingly advise the companies. Need your kind advice and guidance over the matter. Kindly consider this written reply as appearance in Personal Hearing scheduled on 19-04-2022. Assuring you for our utmost cooperation in this regard. Thanking you in anticipation.
7.	**M/s Nenza Pharmaceutical Pvt Ltd**	With reference to your letter No.F.3-2/2022-Reg-I (M-317)(Misc) dated 06-04-2022. Kindly note that our products Dicloned-k 75mg, Movom-p caps 75mg and 100mg have never been in any reported safety and efficacy issue in the country since its production and providing relief to number of patients since its launch for decades. Furthermore, we have inventory of raw and packaging material along with finished stock for sale to market, therefore we request to kindly provide an appropriate time line to consume the inventory of the stated products.
8.	**M/s Shrooq Pharmaceuticals Pvt Ltd**	In reference to your letter No. Nil dated 6th April, 2022, it is hereby noted that I have received show cause notices for cancellation of registration of the products mentioned above. In many defense, I would like to state the following: 1. Diclofenac Potassium in 50mg is registered in Reference Regulatory Authorities while 75mg is not registered. This does not mean that 75mg is unsafe in any way. 2. As discussed earlier in a meeting with DRAP, regarding this matter it was said that 75mg dose is nephrotoxic while a 75mg Ampoule of Diclofenac Sodium is registered in RRAs. 3. We obtained the registration of said products in 2015 and it has been in use by patients all over Pakistan ever since. We have not received a single complaint till this day for any adverse reaction occurring. For the safety of patients, it is requested; please conduct multicenter clinical trials for this dosage form. If there is any evidence of adverse effects, we will happily withdraw these products from the market and you may de-register.

9.	**M/s Fassgen Pharmaceuticals**	With reference to your letter No.F.3-6/2021-Reg-I (M-313)(Misc) dated 7th Jauray, 2022 on received 14th January, 2022, show cause and personal hearing notice regarding cancellation of registration of Flexura 75mg (Diclofenac Potassium) tablets. Worldwide research recommended dosage of Diclofenac Potassium is 150mg.day which provide better relief to patient. So, our product is 75mg it can be divided doses 75mg twice a day. Whereas DRAP earlier decided that, molecules being established since 10 years reported no safety issues should be granted permission to continue for marketing. Furthermore, in our opinion that, letter contents should have been for new manufacturers and not mandatory for every manufacturer. And if the DRAP consider that the permission has to be given according to the international standards and if everyone's registration above 50mg in Pakistan has to be cancelled then it is humble requested you to kindly grant us alternate new product registration. Your cooperation will highly be appreciated.
10.	**M/s Trison Research Laboratories Pvt Ltd**	Kindly refer to your letter No.F.5-3/2022-Reg-II(M-317)(Misc) received by us on 23-04-2022 regarding the subject captioned above. It is stated that decision of the registration board regarding cancellation of the registration of our product TRICLO K 75ng Capsule and the subsequent personal hearing notice cannot be justified on the basis of Reference Regulatory Authority of the said strengths. Many of the pharmaceuticals industries including us in Pakistan are holding the registration of Diclofenac Potassium formulations above 50mg strengths. They are manufacturing the strengths of Diclofenac Potassium above 50mg from their date of registration, no health threatening ADR's relating its safety and efficacy have been observed since then. Moreover, strengths above 50mg are also registered and manufactured in countries like India, China and Bangladesh. Clinical trials have been conducted; its clinical safety and efficacy have been found satisfactory in these countries. Its safety and efficacy in strengths above 50mg cannot be justified by their presence or absence in RRA. So, it is requested to give us exception to personnel hearing notice in the light of the above.
11.	**M/s Caliph Pharmaceuticals (Pvt.) Ltd, KPK**	With due respect, It is stated with reference to your letter subjected above we M/s Caliph Pharmaceuticals do herby state that the subject Drug diclofenac Potassium 75mg is being sold in Pakistan for more than 10 years and our product Caldic 75mg is also being regularly prescribed by doctors around Pakistan since our registration. We therefore request the honorable Registration board to allow the sale of drug in Pakistan. In Case of refusal of this request, we shall apply for Standardization of Formulation as or Strength as per the procedure available in 283rd meeting of Registration Board, till then we shall be allowed to manufacture this drug till we get the approval for diclofenac potassium 50mg which is available in reference Regulatory Authority. We are available for any further information regarding this matter.
12.	**M/s Hilton Pharma (Pvt.) Ltd, Karachi**	We have received your letter No. F 3-6/2021 Reg-1 (M-313) Mis dated 29th December, 2021, referring the subject product case is fixed for personal hearing dated 10th January 2022 at 10. 00am This is to inform you that due to short notice of hearing and paucity of time, we request you to kindly grant an adjournment which is fixed on date cited above so that, we can some with proper hearing.

13.	**M/s Mediate Pharmaceutical (Pvt.) Ltd Karachi**	With reference to your letter No. F 3-6/2021 Reg -1 (M-313) Misc dated the 29th December 2021 received on 05th January 2021 regarding the captioned subject. As per your direction regarding cancelation of the already registered drugs contains Diclofenac Potassium in strength higher than 50mg for our products diclofenac potassium 100mg with registration No 053260 and diclofenac potassium 75mg with registration No. 073586. Kindly note that we are manufacturing 50mg and 100mg of tablets from 2009, we have note receive we have not received any complain regarding dosage of this product. Furthermore, we have not manufactured Defenac 75mg capsule yet, But any how whatever DRAP have decided for all we accept the decision accordingly.
14.	**M/s Zanctok Pharamceutixcals Laboratories Karachi**	In reference to the above mentioned subject i.e the issued by DRAP on 29th December 2021 regarding Registration status of formulation (Diclofenac Potassium 75mg and famotidine 10mg/5ml) which nullifies the registration of these drugs by regulatory authority. It is stated that, our product "Painogin 75mg" was registered by DRAP on 31st July 2009 under section 7 of the drug Act 1976 and Rules 28, 29 and 30 of the Drug (Licensing Registration and Advertising) Rules, 1976 and was recently granted renewal of registration on 24th June 2019 (Ref Paid Challan No. 1936384) and endorsed by Assistant Director Revenue (B&A) DRAP, on 2nd July 2019, In the period of 2009-2021, a total of 91 batches of painogin (Diclofenac Potassium 75mg) were manufactured and marketed throughout the country. During this marketed period, not even a single significant complaint clinical complication, contraindication, product recall or patient relate adverse event was reported. The product is being continually use by the customers with fulfillment of standard safety and dosage requirements. Keeping in view all the above mentioned facts, it is requested to the authority that kindly, as per Registration Board policy , revise the decision of immediate cancellation of registration for this product, and do allow us its manufacturing and marketing on continue basis.

Proceedings during 317th Meeting:

1. The instant proceedings have been undertaken in pursuance of decision taken by the Registration Board in its 313th Meeting wherein Show Cause Notices were issued to all registration holders of Diclofenac Potassium 75mg and 100mg under Section 7(11)(d) of the Drugs Act, 1976 for suspension or cancellation of registration of the aforementioned registered drug products in the public interest. Show Cause to registration holders of the drug in question were also issued personal hearing notices under Section 42 of the Drugs Act, 1976 and were heard at length.

2. A list of pharmaceutical companies which did not attend the meeting is at Annexure-A; a list of pharmaceutical manufacturers who have shown satisfaction on instant proceedings undertaken by the Registration Board, without raising any challenge to the show cause notice and consented to accepting the decision of the Registration Board is at Annexure-B; a list of pharmaceutical companies who either attended personal hearing or responded through written arguments is at Annexure-C; a list of pharmaceutical companies who have filed Writ Petitions before the Hon'ble Lahore High Court, Lahore is at Annexure-D.

3. For the sake of brevity and to avoid repetition, all arguments advanced by the registration holders are amalgamated. The arguments raised in brief in replies to the notice as well as during personal hearing were that the Board in its 313th Meeting without conducting any

proper fact finding enquiry decided to issue show cause notices by disregarding that many registrations of the drug had subsisted for more than a decade without any reported adverse effects; similarly, the show cause notice and personal hearing notices were also devoid of reasons and hence the same are *void ab initio*. The Board had granted registration of drug after satisfying itself of its safety and efficacy and cannot now take a somersault. Non-registration or unavailability of a drug in Reference Regulatory Authorities is an irrational ground for questioning the safety and efficacy of drugs since these have proved effective in the domestic market for years; furthermore, the aforementioned ground is alien to the drug laws and cannot be invoked for any regulatory action. Reference was made to an email by the Denmark Regulatory Authority which expressed its consent to potentially granting registration of diclofenac potassium of dosage above 50mg, to argue that the drug is available in Reference Regulatory Authorities. Reference was also made to British National Formulary as well as other literature to argue that the dosage and administration regime of the Diclofenac Potassium is more than 100 to 150mg and the drug in question falls within the said range. Lastly, it was argued that discontinuation of the drug would adversely affect the patients along with incurring immense financial loss upon the registration holders.

4. Record has been perused with the able assistance of the representatives of the registration holders and arguments have been heard. Since common questions of law and facts are involved, therefore, all notices are decided through a common order.

5. Succinctly stated the facts of the matter are that the Registration Board in its various meetings considered the cases of, *inter alia*, Diclofenac Potassium Tablets/ Capsules in strengths greater than 50mg i.e. the drugs in question. It was concluded that from the available record and review of information available from the Reference Regulatory Authorities ('**RRAs**') that no clinical data regarding their safety and efficacy is available in the above strengths/dosage forms. Hence, continuing registration of the formulations was not considered justifiable keeping in view safety and efficacy parameters which are mandatorily required for continuing with registration of any drug. Therefore, it was decided in the 288th Meeting of the Board dated 14th-15th February, 2019 to issue Show Cause Notices to the registration holders in accordance with the law explained above, to seek response as to why the registrations should not be cancelled or suspended.

6. In the meanwhile, DRAP Authority in its 70th Meeting held on 05-09-2019 decided the following:

   "For formulations containing "drugs" which were previously registered by the Registration Board and have proof of availability and prescription of last 10 years but are not available in the Reference Regulatory Authorities shall continue to be considered/ registered as drugs until and unless withdrawn on Safety, Efficacy and Quality reasons."

7. Subsequently, Registration Board in its 296th Meeting held on the 8th-10th September, 2020, decided to request the DRAP Authority to review its above mentioned decision in the following words:

   "Since, all such formulations which are not approved by the Reference Regulatory Authorities; the safety and efficacy profile cannot be established in the absence of a well-established system for reporting of adverse events, so a reference shall be forwarded to DRAP's Authority with the request to review the decision taken in its 70th meeting held on 05-09-2019. In this regard, PE&R Division shall prepare a comprehensive document/agenda for consideration of Authority, keeping in view the practices adopted by RRA for all such formulations;"

8. The DRAP Authority in its 128th Meeting held on 14-12-2021 was pleased to accept the request the Registration Board and reviewed its 70th Minutes in the following words:

The Authority endorsed the recommendation of Registration Board and made following decisions:-

A. Partially reviewed its earlier decision taken in its 70th meeting held on 05-09-019, consolidated amended decision is reproduced as under:

[…]

4. Drug formulations/ strengths which are previously registered by the Registration Board but are not available in any Reference Regulatory Authorities, shall be reviewed and disposed of keeping in view of safety and efficacy evidence/ data in the reference Regulatory Authorities."

9. In pursuance of the above mentioned, Registration Board in 313th Meeting decided to issue Show Cause Notice to all registration holders of Diclofenac Potassium 75mg and 100mg under Section 7(11)(d) of the Drugs Act, 1976 for cancellation or suspension of registration of the aforementioned in the public interest. Therefore, the instant proceedings are being undertaken in light of permission granted by the DRAP Authority in its 128th Meeting.

10. It is to be noted at the outset that registration or licensing has been held by the Superior Courts to be a privilege not a right which can always be cancelled or suspended in accordance with the law. It has argued at length that the Registration Board granted registration after determining safety, efficacy and quality of drugs which was renewed over time, therefore, the Board cannot after passing of many years re-assess the safety and efficacy of drugs. The argument is fallacious as Rule 27 of the Drugs (Licensing, Registration and Licensing) Rules, 1976 ('**Rules, 1976**') while providing the duration of drug registration also added that the registration can always be cancelled or suspended earlier as well. The grounds on which the drug registration can be suspended or cancelled are provided in Section 7 (11) of the Drugs Act, 1976, and therefore, the argument that registration once granted will continue in perpetuity is against the law. Furthermore, Section 21 of the General Clauses Act, 1897, grants the Board the power to rescind any drug registration in accordance with the grounds provided in Section 7 (11) of the Drugs Act, 1976. The argument in discussion is also fallacious for the reason that scientific pharmaceutical knowledge is always in the process of evolution and decision based on knowledge available at one point of time cannot be used to defeat the just and fair decision to be taken in future with the broadening of knowledge. This principle has been encapsulated in Rule 30 (12) of the Rules, 1976, which grants the Board power to seek any information at any point in time post-registration regarding the safety, efficacy and quality of drugs. The Board has ample powers under Rule 30 (2) to rescind, vary or modify any decision taken by it in the larger public interest to perform its statutory regulatory duty of ensuring the provision of safe and efficacious drugs and medicines to the public at large.

11. The primary ground which has prevailed with the Board for initiating the instant proceedings is that the drug in question (Diclofenac Potassium 75mg and 100mg) is neither approved by any of RRAs nor any data regarding their safety and efficacy is available. To better appreciate the argument, it is important to understand the scheme of the law which allows for placing reliance on RRAs as well as its importance for performing the statutory regulatory duties.

12. Applicant companies are generic drug product manufacturers. The generic drug product is pharmaceutically equivalent to the innovator's drug product as it contains the identical medicinal ingredients in the same amount/strength and dosage form and it must have same pharmacokinetics, pharmacodynamics, indications, contraindications, side effects etc. A generic drug product must work in the same way as that of innovator's drug product and, therefore, it can be interchanged with the innovator's drug product. Diclofenac Potassium, in 75mg and 100mg, has no innovator and applicant companies have neither conducted

nor provided any safety and efficacy study to establish the aforementioned points (i.e., pharmacokinetics, pharmacodynamics, indications, contraindications, side effects etc.).

13. Criteria for grant of registration of any drug product is safety, efficacy and quality parameters and the onus for provision of relevant data to establish aforementioned parameters under the applicable law is upon the applicant/registration holder. For this purpose, applicant either needs to provide sufficient data to satisfy the aforementioned parameters by themselves, or provide reference to approval of registration granted by any Reference Regulatory Authorities ('**RRAs**'); this serves the purpose for determining safety and efficacy of the drugs. RRAs are regulatory authorities of developed countries which have stringent regulatory regimen and have developed robust mechanisms for determining drug safety, efficacy and quality and their decisions are supported by the rapid advances in sciences as well as empirical studies. Even WHO supports the reliance by developing countries on decisions of the Stringent Regulatory Authorities to ensure availability of quality assured, safe and effective health products and to avoid redundancy, global harmonization of standards and wastage of limited regulatory and financial resources. This reliance enables Registration Board and DRAP to have evidence for robust, accurate and evidence based decision-making, considering that the products registered and sold in the countries of RRAs have already been strenuously evaluated to fulfil the harmonized standards of safety, efficacy and quality as adopted by WHO, ICH, etc. This reliance also enables DRAP being the national regulatory authority in undertaking post marketing surveillance, particularly of matters related to safety and efficacy of drug. RRAs have stronger reporting and information sharing system, which can be used by DRAP as a national regulatory authority as a useful tool for surveillance, new available treatments and new indications or contra-indications.

14. It is pertinent to mention that since adoption of RRA, DRAP has approved only those drug products which are either approved by RRAs based on their safety and efficacy assessment or after provision by the applicant pharmaceutical concern of relevant data regarding their safety, efficacy and quality. Moreover, DRAP has also started review process of already registered drugs to ensure availability of quality assured safe and effective therapeutic goods to ailing patients in the larger public interest.

15. The Registration Board in accordance with the global best practices, in its 275th Meeting held on 25th to 27th October, 2017, decided to adopt the RRAs and their decisions "as reference for molecules/ formulations as reference for molecules/ formulations (in same dosage form and strengths) along with clinical trials for human purpose"; this decision was also upheld by the DRAP Authority in its 128th meeting. The aforementioned decision has since been applied by the Registration Board and also been followed by all pharmaceutical concerns for registration of their products without any caveat. Currently, all registered formulations and dosage of drugs and medicines in Pakistan are now required to comply with the details/ specifications as approved by RRAs or provide sufficient data for assessing safety, efficacy and quality of the drug product. Aforementioned decision has been taken to ensure availability of quality assured safe and effective medicines to ailing patients as it is matter of prime public health concern.

16. The adoption of RRAs allows the performance of the statutory duty to "adopt […] standards and guidelines to ensure safety, efficacy, and quality of therapeutic goods" as ordained under Section 7 (t) of the DRAP Act, 2012. Therefore, the DRAP Authority *[created under Section 2 (iv) and Section 7 of the DRAP Act, 2012]* also approved the policy of reliance on RRAs in its 73rd Meeting held on 06-11-2019. Hence, the argument that reliance on RRAs is alien to the drug laws and without any basis for determining safety and efficacy of drugs is baseless. Furthermore, as all pharmaceutical concerns are effectively complying with decision by the Board regarding reliance on RRAs in approval of their drug products and have never raised any objection or caveat to it, therefore, they

are restrained and estopped by their own conduct from challenging it in the instant proceedings.

17. As the legality of reliance on RRAs has been detailed above, the Board has undertaken a thorough inquiry of the registration and availability of Diclofenac Potassium 75mg and 100mg Tablets in RRAs. The findings of the inquiry are summarized below:
    a. Diclofenac potassium is approved by various RRAs in 12.5mg, 25mg and 50mg tablet strengths. As per the review of databases of all RRAs approved by the Registration Board in its 275th meeting, it was observed that the maximum strength of diclofenac potassium in any dosage form is 50mg.
    b. Product monographs and SmPC of innovator's and generic versions of Diclofenac Potassium tablets approved by various RRAs have been reviewed, which depicts that the daily dose of diclofenac potassium is from 75-200mg in divided doses, whereas the maximum strength of available diclofenac potassium tablet is 50mg.
    c. Detailed recommendations of diclofenac potassium regarding dosage as available in the official print and online media of various RRAs have been reproduced as under:

S/N	RRA/ Product Detail	Recommended Dosage
1.	**USFDA/** Cataflam 50mg Tablet	**Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.** • For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg three times a day. With experience, physicians may find that in some patients an initial dose of 100 mg of CATAFLAM, followed by 50 mg doses, will provide better relief. • For the relief of osteoarthritis, the recommended dosage is 100-150 mg/day in divided doses, 50 mg twice a day or three times a day. • For the relief of rheumatoid arthritis, the recommended dosage is 150-200 mg/day in divided doses, 50 mg three times a day or four times a day. • Furthermore, USFDA under the heading of 'warning' states as under: *"Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.* ***Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation.*** *Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.* ***No information is available from controlled clinical studies regarding the use of CATAFLAM in patients with advanced***

		renal disease. *The renal effects of CATAFLAM may hasten the progression of renal dysfunction in patients with pre-existing renal disease (USFDA)."*
2.	**MHRA**/ Diclofenac Potassium 50mg	**Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.** • The recommended daily dose is 100-150mg in two or three divided doses. For milder cases, 75-100mg daily in two or three divided doses is usually sufficient. • In migraine an initial dose of 50mg should be taken at the first signs of an impending attack. In cases where relief 2 hours after the first dose is not sufficient, a further dose of 50mg may be taken. If needed, further doses of 50mg may be taken at intervals of 4-6 hours, not exceeding a total dose of 200mg per day.
3.	**TGA**/ Voltaren Rapid 50mg Tablet	**After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.** • <u>Acute pain states with an inflammatory component:</u> As a rule, the initial daily dosage for adults is 100 to 150 mg. In milder cases, as well as for children over 14 years of age, 75 to 100 mg daily is usually sufficient. The total daily dosage should generally be prescribed in 2 or 3 fractional doses. Treatment is to continue for a maximum of 7 days. If the pain has not resolved satisfactorily after 7 days' treatment, the patient should be instructed to return for review by the doctor. • <u>Acute migraine</u> In migraine, an initial dose of 50 mg should be taken at the first signs of an impending attack. If the pain is not relieved within 2 hours of this initial dose, a further dose of 50 mg may be taken. If needed, further doses of 50 mg may be taken at intervals of 4-6 hours. The total dose to treat an acute migraine should not exceed 200 mg. The total daily dose should not exceed 200 mg. Diclofenac potassium should not be used for migraine prophylaxis. • <u>Symptomatic treatment of primary dysmenorrhoea</u> In primary dysmenorrhoea, initially a dose of 50 or 100 mg should be given followed by 50 mg three times daily for 3 days. Treatment should be started upon appearance of the first symptoms and, depending on their duration and severity, continued for up to three days. If the pain has not

		resolved satisfactorily after 3 days' treatment, the patient should be instructed to return for review by the doctor.
4.	**Health Canada**/ Pms-Diclofenac K	**As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.** • The recommended daily dose for pms-DICLOFENAC K is one 50 mg tablet, every 6-8 hours as required for a total daily maximum amount of 100 mg. • For primary dysmenorrhea, treatment may be initiated on the first day with a loading dose of 100 mg, followed by 50 mg every six to eight hours after the initial dose if needed, for a maximum dose of 200 mg only on the first day. • Patients should be maintained on the lowest effective dose.
5.	**Swedish Medical Products Agency**/ Voltaren T 50 mg Tablet	**Voltaren T treatment should be initiated at the lowest presumed effective dose, in order to be able to adjusted for therapy responses and possible side effects.** **Side effects can be minimized by using the lowest effective dose for the shortest possible duration of treatment that is necessary to control symptoms. In long-term treatment, a low dose is sought.** <u>For Adults:</u> • 50 mg up to 3 times per day. The maximum recommended daily dose is 150 mg. • In migraines, 50 mg is initially given at the first sign of a seizure. If relief is not achieved within the 2 hours, given an additional 50 mg. This can be repeated at intervals of 4-6 hours, with a maximum 150 mg per day.
6.	**BNF**/ Voltarol Rapid 50mg Tablet	• <u>Pain and inflammation in rheumatic disease and other musculoskeletal disorders</u> Adult: 75–150 mg daily in 2–3 divided doses • <u>Acute gout</u> Adult: 75–150 mg daily in 2–3 divided doses • <u>Postoperative pain</u> Adult: 75–150 mg daily in 2–3 divided doses • <u>Migraine</u> Adult: 50 mg, to be given at onset of migraine, then 50 mg after 2 hours if required, then 50 mg after 4–6 hours; maximum 200 mg per day.

18. A study of the above amply demonstrates that the Registration Board had conducted a thorough inquiry before initiation of the instant proceedings. Based upon the above review and inquiry, following two questions were framed and were communicated for guidance

by the Board to various RRA's including USFDA, Health Canada, MHRA UK, Swedish Medical Products Agency Sweden, TGA Australia and BNF:

c. *Whether diclofenac potassium 75mg or 100mg tablet can be administered twice a day to achieve a maximum daily dose of 150 – 200mg;*

d. *Any relevant clinical data which shows that administration of a single dose of 75 or 100mg diclofenac potassium is safe.*

19. Above regulatory authorities through their official replies concurred with the findings of the Board in its inquiry and their replies are summarized as under:

Regulatory Authority	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response
USFDA	• Tisha Washington • International Program|Strategic Initiatives|OCD • Center for Drug Evaluation and Research • CDERINTLEXEC@fda.hhs.gov	U.S. Food and Drug Administration Tel: 301-796-1019 Tisha.Washington@fda.hhs.gov	24-02-2022

- According to the Orange Book, diclofenac potassium is available in 25mg and 50mg tablets only, whereas diclofenac sodium is also available in 75mg and 100mg delayed release and extended release tablets.
- To provide you with insight on the dosing and dose limitation, the dosing information for Diclofenac sodium enteric-coated tablets of 25 mg, 50 mg, and 75 mg can be found below: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019201s035lbl.pdf
- And for Diclofenac potassium immediate-release tablets of 50 mg below https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020142s021s022lbl.pdf
- *The relevant page of the label of Diclofenac potassium immediate-release tablets of 50 mg is placed below:*

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of Cataflam® (diclofenac potassium immediate-release tablets) and other treatment options before deciding to use Cataflam. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

After observing the response to initial therapy with Cataflam, the dose and frequency should be adjusted to suit an individual patient's needs.

For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg t.i.d. With experience, physicians may find that in some patients an initial dose of 100 mg of Cataflam, followed by 50-mg doses, will provide better relief.

For the relief of osteoarthritis the recommended dosage is 100-150 mg/day in divided doses, 50 mg b.i.d. or t.i.d.

For the relief of rheumatoid arthritis the recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d.

Different formulations of diclofenac [Voltaren® (diclofenac sodium enteric-coated tablets); Voltaren®-XR (diclofenac sodium extended-release tablets); Cataflam® (diclofenac potassium immediate-release tablets)] are not necessarily bioequivalent even if the milligram strength is the same.

HOW SUPPLIED

Cataflam® (diclofenac potassium immediate-release tablets)

50 mg – light brown, round, biconvex, sugar-coated tablets (imprinted Cataflam on one side and 50 on the other side in black ink)

Bottles of 100.....NDC 0078-0436-05

Do not store above 30°C (86°F). *Dispense in tight container (USP).*

Regulatory Authority	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response

Swedish Medical Products Agency	• Ingrid Landberg • Head of department Efficacy and Safety 1 • ingrid.landberg@lakemedelsverket.se	P.O.Box 26, SE-751 03 Uppsala, Sweden Visiting address: Dag Hammarskjölds väg 42 Phone: +46 (0)18-17 46 00, Direct: +46 (0)18 174272 ingrid.landberg@lakemedelsverket.se www.lakemedelsverket.se	28-02-2022

- In Sweden the maximum diclofenac potassium dosage is in general 150 mg per 24 hours, and the recommended dosage is depending on the indication.
- This dosage can in general be divided into several doses.
- Unfortunately, we cannot provide any further data or support to address the two questions asked in your email, since these questions must be answered by the respective MAH for the respective medical product.
- Several issues needs to be considered for each case, for example diclofenac formulation, indication and patient population.

Regulatory Authority	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response
Health Canada	bcansenquiries@hc-sc.gc.ca	Bureau of Cardiology, Allergy and Neurological Sciences BCANS Enquiries / Government of Canada bcans.enquiries@hc-sc.gc.ca Bureau de cardiologie, allergologie et sciences neurologiques Enquêtes BCASN / Gouvernement du Canada bcans.enquiries@hc-sc.gc.ca	10-03-2022

- The Therapeutic Products Directorate (TPD) is the Canadian federal authority that regulates pharmaceutical drugs for human use. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations.
- Health Canada has not authorized a 75 mg or 100 mg tablet of diclofenac potassium. Only the 50 mg diclofenac potassium tablet is available.
- Generally speaking the recommended daily dose is one 50 mg tablet, every 6-8 hours as required for a total daily maximum amount of 100 mg.
- For primary dysmenorrhea, treatment may be initiated on the first day with a loading dose of 100 mg, followed by 50 mg every six to eight hours after the initial dose if needed, for a maximum dose of 200 mg only on the first day.
- Patients should be maintained on the lowest effective dose.
- More detailed information is available for diclofenac potassium products through the Health Canada's Drug Product Database.

- A 50mg powder/sachet formulation of diclofenac potassium is also available, CAMBIA® (diclofenac potassium). CAMBIA® (diclofenac potassium) is indicated for the acute treatment of migraine attacks with or without aura in adults 18 years and older. The maximum recommended daily dose is one sachet (50 mg).
- Health Canada is committed to transparency, and maintains many publicly available sources of information which you may find useful:
  - **The Drug Product Database:** https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
  - **The Drug Product Register:** https://hpr-rps.hres.ca/ for Summary Basis of Decision reports
  - **The Public Release of Clinical Information portal:** https://clinical-information.canada.ca/search/ci-rc
- As Health Canada has not authorized a 75 mg or 100 mg tablet of diclofenac potassium, we therefore suggest that to receive the information you are requesting, you contact manufacturers of these products directly, especially those with marketing authorizations in your country.

Regulatory Authority	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response
UK MHRA **(**Medicines and Healthcare products Regulatory Agency)	• **Annabelle** • **MHRA Customer Experience Centre** • Communications and engagement team • Medicines and Healthcare products Regulatory Agency • RIS.NA@mhra.gov.uk	10 South Colonnade, Canary Wharf, London E14 4PU Telephone 020 3080 6000 gov.uk/mhra	22-03-2022

- In the UK, the recommended maximum daily dose of diclofenac is 150 mg.
- The maximum approved strength of diclofenac potassium in the UK is 50 mg as an immediate release tablet formulation.
- We have no data to support the efficacy or safety of 75 mg or 100 mg strength diclofenac potassium tablets.
- We have approved some products containing 75 mg or 100 mg of diclofenac but as oral modified release formulations. These contain alternative diclofenac salts e.g. diclofenac sodium.

Regulatory Authority	Correspondent Name/ Designation/ e-mail	Contact Detail	Date of response
TGA Australia **(**Therapeutic Goods Administration)	• Liam • **TGA Contact Centre** Regulatory Assistance Section Regulatory Engagement Branch • info@tga.gov.au	Phone: 1800 020 653 Fax: 02 6203 1605 Email: info@tga.gov.au Therapeutic Goods Administration Department of Health PO Box 100 Woden ACT 2606 www.tga.gov.au	07-04-2022

- *Whether diclofenac potassium 75mg or 100mg tablet can be administered twice a day to achieve a maximum daily dose of 150 – 200mg*

In Australia, this product is only registered as a 25mg or 50mg product, so cannot directly comment on this query. The repository of PIs is available https://www.tga.gov.au/picmi-search-facility

- *Any relevant clinical data which shows that administration of a single dose of 75 or 100mg diclofenac potassium is safe.*
  Noting the response to the above, the Product Information would be the source of truth in terms of recommended dosing. The TGA cannot provide any data that was submitted by Australian sponsors for the purpose of evaluations to other parties, including overseas regulators without the sponsor's express permission.
- We would suggest contacting the Australian sponsors directly if they would be willing to share any data that would assist.

20. A review of the above clearly shows that various RRAs acknowledged the unavailability of any data regarding the safety and efficacy of *Diclofenac Potassium above 50mg. The reference to an email by the* Denmark Regulatory Authority in which it allegedly argued that registration of the drug in not banned, is also misplaced: the said Regulatory Authority merely expressed its willingness to register it subject to the availability of data regarding its safety and efficacy including clinical trial studies. Had the drug been freely available in Denmark or any other regulatory jurisdiction, the already existing registration status of any drug must have been shared with the Board during the hearing. Reference was also made to the registration of the drug in China, India, Egypt and Kenya. However, these jurisdictions are not comparable to RRAs and thus, their decisions cannot be safely relied on for safety, efficacy and quality parameters as their regulatory authorities are not stringent regulatory bodies. Moreover, none of registration holder were able to share any clinical data on the basis of which these regulatory authorities (China, India, Egypt and Kenya) had purportedly approved the drug. In taking high risk decisions such as determining the safety and efficacy of drugs, the globally accepted principle is to err on the side of caution and adopt the most stringent standards in the largest public interest. The Superior Courts in Pakistan have in various pronouncements held matters related to safety and efficacy of drugs to be directly affecting the constitutionally protected right to life of the people for which highest care and caution is to be adopted by the regulatory authority. It has also been held by the Hon'ble Court that in matters which affect the life and health of the people at large, precautionary principle is to be mandatorily adopted wherein the larger public interest must always give way to narrow corporate interests.

21. *It is to be noted that data regarding safety and efficacy of* Diclofenac Potassium above 50mg *has not been provided by the registration holders in spite of the fact that under the law i.e.* Rule 30 (12) of the Rules, 1976, *the burden of proof is upon the person seeking to continue registration of the drug to advance data regarding its safety and efficacy. It has been argued that the said drug has been freely available in the domestic market for years without any adverse effect being reported, which is proof enough of its safety and efficacy. However, no applicant was able to share evidence of any functional adverse drug reporting system (pharmacovigilance system) to collect such data by their company. In such a situation when the pharmaceutical concerns do not even operate any system to receive and act upon adverse effects of the drugs, the absence of data regarding adverse effects might be the result of lack of reporting rather than an evidence of drug's safety and efficacy. Even otherwise, the absence of any adverse effects at one point of time is not a guarantee that they might not arise in the future and the statutory task of the regulator is to pre-emptively deter such a situation from ever occurring by applying the pre-cautionary principle.*

22. *It is also to be noted that pharmacovigilance data or even stability studies data is not the substitute of positive data regarding the safety and efficacy of drugs which has been*

universally accepted to arise only from valid clinical trials to be performed in accordance with the Bio-Study Rules, 2017. In light of the above discussed, allowing the registration of Diclofenac Potassium above 50mg to continue shall not be in the public interest as statutory intent of enacting the drug laws is the provision of safe and efficacious drugs and medicines to the people at large without any compromise. The task of the regulator is to curb any potential future menace from adversely affecting the public at large rather than responding belatedly to public health crisis which could have been mitigated by applying the pre-cautionary principle.

23. It was also argued with reference to British National Formulary as well as other literature that the maximum daily dosage and administration regime of the Diclofenac Potassium is between 100 to 150mg and the drugs in question falls within the said range. The argument cannot sustain as the literature emphasizes the "use of lowest effective dose for the shortest duration". Indications where 100mg is recommended are only dysmenorrhea or pain, and even in such cases the same is mentioned as either initial dose or loading dose (meaning that 1 dose only and no subsequent dose intake); such requirement can be met by taking two tablets of 50mg and it is for this reason that the RRAs have not approved Diclofenac Potassium in dosage above 50mg. Therefore, there is no medical necessity for Diclofenac Potassium above 50mg. Furthermore, in case of suspension of registration, there will be ample supply of registered 50mg dosage form to meet the patient needs.

24. Representative of M/s Hilton Pharma, Karachi during arguments relied upon an academic study titled "Diclofenac Potassium in Acute Postoperative pain and Dysmenorrhoea results from comprehensive Clinical Trial Reports". However, a basic review of the article shows that it is neither published in a peer reviewed academic journal of repute nor is there any evidence that any RRA across the world has endorsed its contents while making its regulatory decision. Furthermore, the article does not have any data regarding safety and efficacy of Diclofenac Potassium above 50mg. Therefore, safe reliance cannot be made on it.

25. M/s Pakheim Lahore, in their written response, submitted that their product Fen-K SR is a sustained release tablet unique release profile that extends upto 10 hours and during clinical trials on different volunteers it has been recorded that ratio of diclofenac potassium in blood stream do not rise above 5.5 after 8 hours of ingestion which is within the normal range and safe (Data of clinical trials will be submitted if desired). The firm further offered DRAP to conduct clinical trials from any of the DRAP recommended laboratory. However, the firm has neither submitted any information regarding protocols of the study conducted by them nor any detail stating that the clinical trials have been performed in compliance with the Bio Study Rules, 2017. In the absence of such information, legitimacy of the so called clinical trials cannot be established rather these are in-vitro and in-vivo studies of the product and don't depict any safety and efficacy profile of the product in any way.

26. M/s Alfalah Pharma, Lahore, in their written response, submitted that they have conducted stability studies on three different batches at both accelerated (40°C ± 2°C and 75% + 5% RH) and real time (30°C ± 2°C and 65% + 5% RH) conditions with satisfactory results achieved. Stability studies can be used as one of the tool/parameter to determine quality of a drug product but are not relevant to establish safety and efficacy of the product.

27. The Board noted that evidence based regulatory decisions are being taken in the larger public interest and only against registration of Diclofenac Potassium above 50mg (75mg and 100mg) due to lack of its safety and efficacy data and pharmaceutical firms can obtain

registration of Diclofenac Potassium for 50mg, 25mg and 12.5mg Tablet and 50mg Sachet after completion of legal formalities. This will preserve them from any financial loss as they can serve the patients in dosage forms with evidence based safety and efficacy profile of drug products.

28. Director DTL Karachi dissented with the decision taken by the Board and opined not to suspend registration of these products.

Decision:

In light of the foregoing discussions, risk-benefit analysis and public health impact of Diclofenac Potassium 75mg and 100mg, the Board made following decisions:

i. Suspended all drug registrations of Diclofenac Potassium 75mg and 100mg under Section 7 (11) (d) read with Section 42 of the Drugs Act, 1976 in the larger public interest, with immediate effect as these are neither approved by any Reference Regulatory Authority nor any safety and efficacy data regarding them is available with any registration holder. Period of suspension will be for one (01) year or till demonstration of its safety and efficacy by conducting indigenous clinical trials in accordance with the Bio Study Rules, 2017 or its approval by the Reference Regulatory Authorities, whichever is earlier. After provision of aforementioned data, cases of such pharmaceutical firms shall be considered on merit by Registration Board.

ii. Suspended manufacturing and import of these drug products immediately and directed to withdraw available stocks from the market in the larger public interest. QA&LT Division, DRAP will monitor and implement the decision in coordination with the respective provincial governments.

iii. Recommended Licensing Division, DRAP for approval of Qualified person for Pharmacovigilance (QPPV) / Local Safety Officer (LSO) whichever is applicable in licensed pharmaceutical units and advised PE&R and BE&R Divisions for implementing similar action for importers of finished drug products as required under Pharmacovigilance Rules, 2022.

iv. Final decision regarding pharmaceutical firms who have obtained interim relief from the Hon'ble Lahore High Court, Lahore shall be announced after decision and direction by the Hon'ble Court. Legal Affairs Division is requested to place the instant decision before the Hon'ble Court and seek expeditious disposal of the matter in the larger public interest.

v. Recommended DRAP Authority for out of queue consideration of registration applications of Diclofenac Potassium 50mg, 25mg and 12.5mg Tablet and 50mg Sachet in order to facilitate the registration holders affected by the instant decision.

Annexure-A

Non-Attendees	
Sr. No.	**Registration Holder**
1.	3S Pharmaceuticals (Pvt) Ltd., 5-Km, Off Raiwind Manga Road, Lahore.
2.	M/s. Alen Pharmaceuticals (Pvt) Ltd., 138 Nowshera Industrial Estate, Risalpur.
3.	M/s. Alkemy Pharmaceutical Laboratories (Pvt) Ltd, Hyderabad, P-9 SITE, Hyderabad.
4.	M/s Alliance Pharmaceuticals (Pvt) Ltd, Plot # 112-A, Hayatabad, Industrial Estate, Peshawar.
5.	M/s. Alson Pharmaceuticals, 169, Road No.7-B, Industrial Estate Hayatabad, Peshawar.
6.	Amarant Pharamceuticals (Pvt) Ltd., 158-D Den Toro Gadap Road Super Highway Karachi., Karachi Previous Title: Lexicon Pharmaceuticals Pvt. Ltd. Karachi
7.	Arsons Pharmaceutical Industries (Pvt) Ltd., 22-Km Multan Road Off 2.5-KM Defence Road, Lahore.
8.	Basel Pharmaceuticals, 227-Phase-II Multan Industrial Estate Multan, Multan
9.	Berlex Lab. International, 10-Km Nangshah Chowk Karachi Road Multan, Multan
10.	Bio Fine Pharmaceuticals (Pvt) Ltd., 74 Industrial Estate Multan.
11.	Caylex Pharmaceuticals (Pvt) Ltd., 27-Km Mian Raiwind Road Lahore.
12.	M/s. Convell Laboratories, Saidu Sharif, Swat.
13.	Crest Pharmaceuticals, Plot No. 43 Industrial Triangle Kahuta Road Islamabad.
14.	Crown Pharmaceuticals, 286 Kahuta Industrial Triangle Islamabad.
15.	M/s Dr. Raza Pharma, Plot No. 44-C, Industrial Estate, Hayatabad, Peshawar.
16.	English Pharmaceutical Industries, Indus Link Katarband Road Thokar Niaz Beg, Multan Road Lahore.
17.	Envoy Pharmaceuticals (Pvt) Ltd., 27-Km Multan Road Maraka Lahore.
18.	E-Pharm Laboratories, A-40, S.I.T.E. Super Highway Industrial Area North, Karachi.
19.	M/s Farm Aid Group, Plot # 3/2, Phase I & II, Hattar Industrial Estate, Haripur.
20.	Ferroza International Pharmaceuticals (Pvt) Ltd., 33-Km Ferozepur Road Lahore.
21.	Festal Laboratories, Jinnah Industries Link Kattar Band Road Thokar Niaz Baig Lahore.
22.	M/s Fozan Pharmaceutical Industrial (Pvt) Ltd.,36- A, Industrial Estate, Hayatabad, Peshawar.
23.	Friends Pharma (Pvt) Ltd., 31-Km Ferozepur Road Lahore.
24.	M/s Genome Pharmaceuticals (Pvt.) Ltd. Plot # 16/I-Phase IV, Industrial Estate, Hattar, Haripur Previous Title: Silver Oak Corporation, Plot No.16/1-Phase IV, Industrial Estate, Hattar
25.	Harmann Pharmaceutical Laboratories (Pvt) Ltd., 16-Km Multan Road Lahore. , Lahore
26.	M/s. Healer Laboratories (Pvt) Ltd., 96/102-C SIE Kohat Road, Peshawar.
27.	M/s High-Q Pharmaceuticals, Plot No.224, Sector 23, Korangi Industrial Area, Karachi.
28.	Hoover Pharmaceuticals (Pvt) Ltd., Plot No.16 Zain Park Industrial Area Saggain By Pass Road Lahore., Lahore
29.	Hygeia Pharmaceuticals, Plot No. 295 Industrial Triangle Kahuta Road Islamabad.
30.	Irza Pharma (Pvt) Ltd., 10.2-Km Lahore Sheikhupura Road P.O Kot Abdul Malik District Sheikhupura.
31.	M/s. Libra (Pvt) Ltd, 77-Peshawar Industrial Estate, Hayatabad, Peshawar.
32.	Mass Pharma (Pvt) Ltd., 17 Km Ferozpur Road Lahore., Lahore
33.	M/s Medicaids (Pvt) Limited, Plot No. 10, Sector-27, Korangi Industrial Area, Karachi.
34.	Mediceena Pharma (Pvt) Ltd., 27 Km Raiwind Road Lahore.
35.	Medicraft Pharmaceuticals (Pvt.) Ltd., 126-B Industrial Estate Hayatabad, Peshawar.
36.	Medisynth Pharmaceuticals, Plot No. 55 Street No. S-5 National Industrial Zone Rawat Islamabad.
37.	M/s. Meditech Pharmaceuticals, 15-D Industrial Estate, Jamrud Road, Peshawar
38.	Murfy Pharmaceuticals (Pvt) Ltd., 8-Km Raiwind Road Lahore.
39.	M/s. Navegal Laboratories, Plot No. 41/1-A-2,Phase-I Industrial Estate, Hattar, Haripur.
40.	M/s Neomedix, Plot No. 5/N-5 National Industrial Zone, Rawat Islamabad.
41.	M/s Noa Hemis Pharmaceuticals, Plot #154, Sector 23, Korangi Industrial Area, Karachi.

42.	M/s. Polyfine Chempharma, 51 Industrial Estate, Hayatabad, Peshawar.
43.	Rasco Pharma (Pvt) Ltd., 5.5 Km Raiwind Road Ali Razabad Lahore.
44.	M/s Ray Pharma (Pvt) Ltd., S-58, S.I.T.E, Karachi.
45.	M/s Raymond Pharmaceuticals Lahore (Formerly Home Chemical Industries), 16-KM Multan Road Lahore.
46.	M/s. Regent Laboratories, C-20, S.I.T.E Super Highway, Karachi.
47.	M/s Safe Pharmaceuticals (Pvt.) Ltd., Plot C-I-20, Sector 6-B, North Karachi Industrial Area, Karachi.
48.	Shawan Pharmaceuticals, Plot No. 37 Road NS-1 National Industrial Zone Rawat Rawalpindi.
49.	Theramed Pharmaceuticals (Pvt) Ltd., 45-Km Multan Road Lahore., Lahore
50.	Venus Pharma, 23 Km Multan Road Lahore. , Lahore
51.	Wilshire Laboratories (Pvt) Ltd ., 124/1 Industial Estate Kot Lakhpat Lahore.

Annexure-B

Attendees Having Agreement with RB Decision			
Sr. No.	**Registration Holder**	**Statement of Agreement**	**Name & Designation of Representative (Attendees)**
1.	Allmed (Pvt) Ltd., Plot No. 590 Sundar Industrial Estate Lahore.	i. Registered for 10 years. ii. They agree with the decision of Registration Board for all registration holders.	Mr. Feroze Ahmad Manager Regulatory Affairs
2.	Axis Pharmaceuticals, 3-B Value Addition City 1.5 Km Khurrianwala – Sahanwala Road Faisalabad.	i. Registered for 10 years. ii. They agree with the decision of Registration Board for all registration holders.	Rana Fakhar Hayat GM Quality, regulatory
3.	CCL Pharmaceuticals (Pvt) Ltd., 62 Industrial Estate Kot Lakhpat Lahore.	They agree with the decision of Registration Board for all registration holders.	Mr. Babar Imran Babar SMCA
4.	M/s Fedro Pharmaceutical Labs (Pvt) Ltd., 149-Industrial Estate, Jamrud Road, Hayatabad.	They agree with the decision of RB and requested to convert their already registered strengths to 50mg.	Mr. Shakeel Ahmad Production Manager
5.	Global Pharmaceuticals, Plot No 204-205 Kahuta Triangle Industrial Area Islamabad.	They agree with the decision of Registration Board for all registration holders.	Mr. Suleman
6.	Medizan Laboratories (Pvt) Ltd., Plot No 313 Industrial Triangle Kahuta Road Islamabad.	They agree with the decision of Registration Board for all registration holders.	Mr. Khalid Mahmood
7.	Qintar Pharmaceuticals, 14-A Small Industrial Estate Lahore Road Sargodha.	They agree with the decision of Registration Board for all registration holders.	Mr. Sufian Sarfraz
8.	Rogen Pharmaceuticals, Plot No. 30 S-4 National Industrial Zone Rawat Islamabad.	They agree with the decision of RB and requested to convert their already registered strengths to 50mg.	Mr. Muhammad Aqil QCM
9.	Siam Pharmaceuticals, Plot No. 217 Industrial Triangle Kahuta Road Islamabad.	i. They agree with the decision of Registration Board for all registration holders. ii. Interpretation of data may be required from multinational company producing said product before final decision.	Mr. Noor Faraz QCM
10.	Swan Pharmaceutical (Pvt) Ltd., 11-E Industrial Triangle Kahuta Road Islamabad.	They agree with the decision of Registration Board for all registration holders	Mr. Awar
11.	M/s Unitech Pharmaceuticals (Pvt) Ltd. Plot No. 4/116, Sector 21, Korangi Industrial Area, Karachi.	They agree with the decision of Registration Board for all registration holders.	Mr. Ikram Habib
12.	Valor Pharmaceuticals, 124/A Kahuta Triangle Industrial Area Islamabad.	They agree with the decision of Registration Board for all registration holders.	Mr. Faisal
13.	Vision Pharmaceuticals, Plot No. 22-23 Industrial Triangle Kahuta Road Islamabad.	They agree with the decision of Registration Board for all registration holders.	Mr. Iftikhar Tarar

14.	Winilton Pharmaceuticals (Pvt) Ltd., Plot No. 45 Street No. S-5 National Industrial Zone Rawat Rawalpindi.	They agree with the decision of RB and requested to convert their already registered strengths to 50mg.	Mr. Amir Afzal Admin
15.	M/s Zanctok Pharmaceuticals Laboratories, F-5 S.I.T.E Area, Hyderabad.	i. The product has already been discontinued on the bases of CDL report. ii. They agree with the decision of Registration Board for all registration holders.	Mr. Ghulam Abbas

Annexure-C

Attendees Having Disagreement/ Varying Stance			
Sr. No.	**Registration Holder**	**Statement/ Stance**	**Name & Designation of Representative (Attendees)**
1.	M/s. Aries Pharmaceuticals (Pvt) Ltd, 1-W, Industrial Estate, Hayatabad, Peshawar.	i. Their product is registered since 2005. They are marketing 60,000 packs per month and no ADRs are reported till now. ii. Reference was made to the decision of 70th meeting of Authority regarding 10 years policy. iii. In response to question asked it was replied that no QPPV has been appointed. Safety efficacy data is not available with the firm.	Mr. Yasar Siddique
2.	Batala Pharmaceuticals, 23/B Small Industrial Estate No. 2 Near Wapda Town, Khiali Bypass Gujranwala.	i. Their product is registered since 2003 and no ADRs are reported till now. ii. It covers 60-70% of total market of firm and in case of cancellation their market will badly suffer. iii. In response to question asked it was replied that no QPPV has been appointed. Safety efficacy data is not available with the firm.	Mr. Yousaf CEO
3.	Benson Pharmaceuticals, Plot No.119 Street No.8, I-10/3 Industrial Area Islamabad.	A System for Clinical trials should be established and trials be conducted from CRF otherwise firms may be allowed to continue the production.	Mr. Javid Iqbal CEO
4.	Biorex Pharmaceuticals, Plot No.292 Industrial Triangle Kahuta Road Islamabad.	i. Their product is registered since 2010 and no ADRs are reported till now. ii. Reference was made to the decision of 70th meeting of Authority regarding 10 years policy. iii. Reference was made to BNF.	Mr. Muhammad Ramzan QCM
5.	Caraway Pharmaceuticals, Plot No. 12 Street No. N-3 National Industrial Zone (RCCI) Rawat Islamabad.	Registered for 15years and no ADRs are reported till now.	Dr. Sayed Tauqeer Ali Chief Operating Officer
6.	M/s. Gillman Pharmaceuticals, 14/2-A. Phase I & II, Industrial Estate, Hattar.	i. Their product is registered since 2010 and no ADRs are reported till now. ii. In case of cancellation their institutional business will suffer.	Mr. Rauf Regulatory Manager
7.	Glitz Pharma, Plot No 265 Industrial Triangle Kahuta Road Islamabad.	i. In USFDA officially this strength is not banned ii. Converted in 2015 from OTC to perception only medicine. iii. Higher doses more effective iv. Novartis replied that only due to due to commercial reasons	Miss. Arifa Hibba QA

		these strengths are not manufactured.	
8.	Goodman Laboratories, Plot No.5 St: No. S-5 National Industrial Zone Rawat Islamabad.	i. Same products are registered in India and Kenya. ii. DRAP should conduct clinical trials for safety efficacy of Diclofenac Potassium.	Mr. Zubair Saeed Production Incharge
9.	Hamaz Pharmaceuticals (Pvt) Ltd., 13-Km Lutafabad Bosan Road Multan.	i. Their product is registered since 2009 and no ADRs are reported till now. ii. In response to question asked it was replied that no QPPV has been appointed. Safety efficacy data is not available with the firm. iii. They have submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). iv. Main component is diclofenac in both formulations which is available in 75mg and 100mg in salt form of sodium. v. In China, India, Egypt diclofenac potassium is available in strengths above 50mg which covers 38% of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. vi. They have also consulted following RRAs regarding registration of Diclofenac potassium above 50mg and their responses are as under; vii. Sweden: application for registration of said product is welcomed. viii. Japan: They can register said product on the basis of Clinical Trials Data. ix. Denmark: Formulation is not banned for registration due to any health and safety reasons. x. In Martindale both salt forms of Diclofenac have same doses. xi. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. xii. Since, the product has not been proven either safe or unsafe, therefore the matter should be investigated on the basis of scientific grounds.	Mr. Atif Shah Regulatory Manager

		xiii. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. xiv. Hence, the said product may not be cancelled and show-cause may be revoked.	
10.	M/s Hicon Pharmaceuticals. 131-Industrial Estate, Hayatabad, Peshawar.	i. There is minor difference in strengths of 50 mg and 75mg. 50mg can be taken four times daily and 75mg can be taken three times daily. ii. Both strengths have different efficacy while toxicity profile is same for both. iii. In Ireland max. daily dose is 225mg.	Mr. Umair Aslam GM Mr. Sahams-Ul-Islam QCM
11.	M/s Hilton Pharma (Pvt.) limited, Plot # 13-14, Sector 15, Korangi Industrial Area, Karachi.	i. With experience, physicians may find that in some patients and initial dose of 100mg of CTAFLAM, followed by 50mg doses, will provide better relief. Hence innovator brand has evaluated a single dose of up to 100mg as safe & well tolerated. ii. In prolonged use for more than 6 months of Diclofenac Potassium, Hepatic Issues are reported. <u>Following review article was shared by the firm:</u> i. **Title:** Diclofenac Potassium in Acute Postoperative Pain and Dysmennorhoea: Results from Comprehensive Clinical Trial Reports ii. **Published** dated 17-01-2018 iii. **Journal:** "Pain Research & Management" (Impact factor: 3.037) iv. **Publisher:** Hindawi v. **Study:** Efficacy of Diclofenac Potassium in unpublished clinical study reports (CSRs) and published reports was compared to examine publication bias, industry bias and comprehensiveness. vi. **Discussion & Results:** There was no clinically important difference in efficacy between 50mg and 100mg doses of diclofenac potassium. vii. **Conclusion:** ***As indicated in results the review article does not provide any sufficient data/ evidence supporting safety and efficacy of diclofenac potassium in strengths above 50mg especially when it has been***	Dr. Imtiaz Ahmad General Manager Medical Affairs

		recommended by various RRAs "to use the lowest effective dose for shortest duration necessary to control symptoms."	
12.	Linear Pharma, Plot No. 18 S. No. S-4 National Industrial Zone (RCCI) Rawat, Islamabad.	Registered since 2010. Same dose for Diclofenac Sodium and Potassium in BNF.	Mr. Zahoor Ahmad QCM
13.	M/s Macter International Limited. F-216, S.I.T.E, Karachi.	i. M/s. Cibex on behalf of M/s. Macter. Representative of M/s. Cibex was advised to submit authority letter otherwise your presence cannot be considered. ii. They have sent an email to Denmark and they have replied that Diclofenac Potassium is not banned for registration due to any health and safety reasons. iii. In China, India and Bangladesh, diclofenac potassium is available in strengths above 50mg which covers half of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. iv. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. v. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. vi. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. vii. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). viii. Hence, the said product may not be cancelled and show-cause may be revoked.	Representative of M/s. Cibex Mr. Malik Zamir appeared on behalf of M/s. Macter. Representative of M/s. Cibex was advised to submit authority letter otherwise your presence cannot be considered but he has not submitted authority letter.
14.	Medley Pharmaceuticals, 41/A Punjab Small Industries Estate Jhang Bahtar Road Wah Cantt., Wah Cantonment	i. Their product is registered since 2009 and no ADRs are reported till now. ii. Reference was made of BNF. iii. In response to question asked it was replied that no QPPV has	Mr. Asad Mughal Production Manager

		been appointed and no ADRs has been reported for any other product.	
15.	Miracle Pharmaceuticals (Pvt) Ltd., Plot No-8 Street No-5 National Industrial Zone Rawat, Islamabad.	They are marketing this product since long and due to cancellation of said product their market will suffer.	Mr. Aftab Safdar Procurement Officer Mr. Naveed Ahamd QCM
16.	Panacea Pharmaceuticals, Plot No.4 Street No. S-6 National Industrial Zone Rawat Islamabad.	i. Their product is registered since 2006 and no ADRs are reported till now. ii. Market survey shall be conducted before final decision.	Representative of firm
17.	Pearl Pharmaceuticals, Plot No 204 Street No. 1 I-10/3 Industrial Area Islamabad.	i. Their product is registered since 2005. They are marketing 60,000 packs per month and no ADRs are reported till now. ii. Reference was made to the decision of 70th meeting of Authority regarding 10 years policy. iii. In response to question asked it was replied that no QPPV has been appointed. Safety efficacy data is not available with the firm. iv. Reference was made to BNF and registrations in India and China.	Mr. Ilyas Jalal Mr. Fayaz
18.	M/s. Saaaf Pharmaceutical Industries, Plot No. 15, Nowshera Industrial Estate, Risalpur.	Their product is registered since 2005 and no ADRs are reported till now.	Mr. Fayaz Khan
19.	M/s Shaheen Pharmaceuticals 3 km, Murghzar Road, Saidu Sharif, Swat.	i. Their product is registered since 2005 and no ADRs are reported till now. ii. In response to question asked it was replied that no QPPV has been appointed and no ADRs has been reported.	Mr. Akbar Zeb QCM
20.	Sunshine Pharmaceuticals, Emanabad, G.T. Road, Gujranwala.	Clinical Trails shall be conducted in collaboration with DRAP.	Adv. Usman Saleem Director Mr. Adil Zaman
21.	M/s Tabros Pharma (Pvt) limited, L-20/B, Sector-22, Federal B Industrial Area, Karachi.	i. In Drugs.com 100mg oral dose is recommended as initial dose. ii. In EMC 100-150mg is recommended in two divided doses.	Mr. Aurangzeb SMRA
22.	Well & Well Pharma (Pvt) Ltd., Plot No.7 Street S-8 National Industrial Zone RCCI Rawat Islamabad.		Mr. Sher Afsar Kahan
23.	Wise Pharmaceuticals, Plot No. 3-A Street S-1 National Industrial Zone, Rawat Islamabad.	i. Their product is registered since 2007 and they are bearing market expenses. ii. Reference was made of BNF. iii. It was requested to allow them to continue production till the	Mr. Syed Mohsin Ali QCM

		establishment of scientific grounds for cancellation.	
24.	M/s Zephyr Pharmatec (Pvt.) Ltd, A-39, SITE II, Super Highway, Karachi.	Scientific study is required to establish safety and efficacy as no ADRs and clinical trial data is available.	Mr. Asif Khitab Sr. Manager regulatory

Firms Responded through Written Arguments

Sr. No.	Registration Holder	Written Statement
25.	M/s. Wnsfeild Pharmaceuticals, Plot.No.122, Block-A, Phase-V,Industrial Estate Hattar, Haripur.	i. In China, India, Kenya diclofenac potassium is available in strengths above 50mg which covers 38% of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. ii. They have also consulted following RRAs regarding registration of Diclofenac potassium above 50mg and their responses are as under; iii. Sweden: application for registration of said product is welcomed. iv. Japan: They can register said product on the basis of Clinical Trials Data. v. Denmark: Formulation is not banned for registration due to any health and safety reasons. vi. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. vii. In Martindale both salt forms of Diclofenac have same doses. viii. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. ix. Since, the product has not been proven either safe or unsafe, therefore the matter should be investigated on the basis of scientific grounds. x. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. xi. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). xii. Hence, the said product may not be cancelled and show-cause may be revoked.
26.	M/s Barrett Hodgson Pakistan (Pvt) Ltd., F/423, S.I.T.E., Karachi.	Our technical person who will participate in case and know all the relevant facts is on leave. Therefore, we urge and request you to kindly defer and grant us an adjournment to a next date of hearing wherein we shall make sure to participate with full facts and evidence of the case under discussion.
27.	M/s Welmark Pharmaceuticals, Plot #122, Block B, Phase 5, Industrial State, Hattar.	i. In China, India, Kenya diclofenac potassium is available in strengths above 50mg which covers 38% of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. ii. They have also consulted following RRAs regarding registration of Diclofenac potassium above 50mg and their responses are as under; iii. Sweden: application for registration of said product is welcomed. iv. Japan: They can register said product on the basis of Clinical Trials Data. v. Denmark: Formulation is not banned for registration due to any health and safety reasons. vi. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary

		dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. vii. In Martindale both salt forms of Diclofenac have same doses. viii. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. ix. Since, the product has not been proven either safe or unsafe, therefore the matter should be investigated on the basis of scientific grounds. x. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. xi. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). xii. Hence, the said product may not be cancelled and show-cause may be revoked.
28.	M/s NovaMed Pharmaceuticals (Pvt) Ltd., 28-Km Ferozepur Road Lahore, Lahore	Registered with the DRAP since 13-06-2006 and 10-08-2010 and are being marketed since registration. However, during this period of 12 years no adverse event has been reported till date. When there is a concern of efficacy and safety of drug, pharmacovigilance department of the competent authority is requested to conduct a risk based study associated with efficacy and safety pf questioned strengths of said drugs and accordingly advise the companies. In Denmark formulation is not banned for registration due to any health and safety reasons.
29.	Medera Pharmaceuticals (Pvt) Ltd., 249-A Industrial Triangle Kahuta Road Islamabad., Islamabad	i.Available in India, China, Kenya and Denmark. ii.Our product holds 30% of the market.
30.	Webros Pharmaceuticals, Plot No. 1 Street No. 10 National Industrial Zone Rawat Islamabad.	i. In China, India, Kenya diclofenac potassium is available in strengths above 50mg which covers 38% of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. ii. They have also consulted following RRAs regarding registration of Diclofenac potassium above 50mg and their responses are as under; iii. Sweden: application for registration of said product is welcomed. iv. Japan: They can register said product on the basis of Clinical Trials Data. v. Denmark: Formulation is not banned for registration due to any health and safety reasons. vi. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. vii. In Martindale both salt forms of Diclofenac have same doses. viii. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. ix. Since, the product has not been proven either safe or unsafe, therefore the matter should be investigated on the basis of scientific grounds. x. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. xi. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11).

		xii. Hence, the said product may not be cancelled and show-cause may be revoked.
31.	M/s Adamjee Pharmaceuticals (Pvt.) Ltd., Plot 39, Sector 15, Korangi Industrial Area, Karachi.	Firm has requested to cancel their products after utilization of packing material of said products.
32.	Alfalah Pharma (Pvt) Ltd., 12-Km, Sheikhupura Road, Lahore.	i. We honor the board decision and it is so correct that there is no approved reference from any RRAs, but it is humbly requested in you honor that we have registered this product since dated 04-06-2009 (copy of registration letter is attached) and we are selling it on doctor's prescription. ii. We have a huge market regarding its use. We had never any complaint from any doctor or patient regarding its use. We had done stability study of three different batches on both Accelerated (40°C 2°C and 75% + 5% RH) and Real time (30°C 2°C and 65% + 5% RH) at different intervals, the results of that are satisfactory (copy attached). iii. Kindly allow us to continue quality production of "LYON 75MG TABLET (Diclofenac potassium)". iv. Your decision is highly appreciated.
33.	M/s Caliph Pharmaceuticals (Pvt) Ltd, Plot No. 17 Industrial Estate, Risalpur, Khyber Pakhtunkhwa.	i. With due respect, It is stated with reference to your letter subjected above we M/s Caliph Pharmaceuticals do herby state that the subject Drug diclofenac Potassium 75mg is being sold in Pakistan for more than 10 years and our product Caldic 75mg is also being regularly prescribed by doctors around Pakistan since our registration. ii. We therefore request the honorable Registration board to allow the sale of drug in Pakistan. iii. In Case of refusal of this request, we shall apply for Standardization of Formulation as or Strength as per the procedure available in 283rd meeting of Registration Board, till then we shall be allowed to manufacture this drug till we get the approval for diclofenac potassium 50mg which is available in reference Regulatory Authority. iv. We are available for any further information regarding this matter.
34.	Candid Pharmaceuticals, Opp Pasrur Sugar Mills Sialkot Road, Pasrur.	We, Candid Pharmaceuticals, hereby submit that any decision taken up by the Drug Registration Board in interest of general public regarding fate of Diclofenac potassium 75mg will be acceptable to us.
35.	M/s. Fassgen Pharmaceuticals,, Plot No. 67/1-A, Phase-III, Industrial Estate, Hattar.	i. Worldwide research recommended dosage of Diclofenac Potassium is 150mg.day which provide better relief to patient. So, our product is 75mg it can be divided doses 75mg twice a day. ii. Whereas DRAP earlier decided that, molecules being established since 10 years reported no safety issues should be granted permission to continue for marketing. Furthermore, in our opinion that, letter contents should have been for new manufacturers and not mandatory for every manufacturer. iii. And if the DRAP consider that the permission has to be given according to the international standards and if everyone's registration above 50mg in Pakistan has to be cancelled then it is humble requested you to kindly grant us alternate new product registration. iv. Your cooperation will highly be appreciated.
36.	Lotus Pharmaceutials (Pvt) Ltd., Plot No.118-A Street No. 8, I-10/3 Industrial Area Islamabad.	We have no intention to manufacture above mentioned product in future.

37.	Mediate Pharmaceutical (Pvt) Ltd. Plot No. 150-151 Sector 24 Korangi Industrial Area Karachi.	i. As per your direction regarding cancelation of the already registered drugs contains Diclofenac Potassium in strength higher than 50mg for our products diclofenac potassium 100mg with registration No 053260 and diclofenac potassium 75mg with registration No. 073586. ii. Kindly note that we are manufacturing 50mg and 100mg of tablets from 2009, we have note receive we have not received any complain regarding dosage of this product. iii. Furthermore, we have not manufactured Defenac 75mg capsule yet, But any how whatever DRAP have decided for all we accept the decision accordingly.
38.	Nenza Pharmaceuticals (Pvt) Ltd., 33-A Hayatabad Industrial Estate Peshawar.	i. Our products have never been in any reported safety and efficacy issue in the country since its production and providing relief to number of patients since its launch for decades. ii. Furthermore, we have inventory of raw and packaging material along with finished stock for sale to market, therefore we request to kindly provide an appropriate time line to consume the inventory of the stated products.
39.	Rotex Pharma (Pvt) Ltd., Plot No. 206-207 Industrial Triangle Kahuta Road Islamabad,	we would like to inform you that the registration of the subject Product i.e. Volden Fort K 75mg Tablet may not be cancelled with immediate effect, because we have the following inventory in hand; iv. Finished Goods in warehouse 38,893 packs v. Diclofenac Potassium (API) in inventory 308kg vi. Diclofenac Potassium (API) LC opened (See attached) 1000kg Therefore, it is requested that we may please be allowed to consume above stock before cancellation of Registration.
40.	Trison Research Labortories (Pvt) Ltd., 27-A Punjab SIE Sargodha.	i. It is stated that decision of the registration board regarding cancellation of the registration of our product TRICLO K 75ng Capsule and the subsequent personal hearing notice cannot be justified on the basis of Reference Regulatory Authority of the said strengths. ii. Many of the pharmaceuticals industries including us in Pakistan are holding the registration of Diclofenac Potassium formulations above 50mg strengths. They are manufacturing the strengths of Diclofenac Potassium above 50mg from their date of registration, no health threatening ADR's relating its safety and efficacy have been observed since then. iii. Moreover, strengths above 50mg are also registered and manufactured in countries like India, China and Bangladesh. Clinical trials have been conducted; its clinical safety and efficacy have been found satisfactory in these countries. Its safety and efficacy in strengths above 50mg cannot be justified by their presence or absence in RRA. iv. So, it is requested to give us exception to personnel hearing notice in the light of the above.
41.	M/s. Z-Jans Pharmaceuticals (Pvt) Ltd., 148-A, Industrial Estate Hayatabad, Peshawar.	It is stated that as per the study submitted by the PPMA to the honorable board our stance will be the same as per PPMA and we will be agreed with collective decision of the honorable board regarding our afore said product if the decision was for all the manufacturer in Pakistan.
42.	Unison Chemical Works, 15 Km Raiwind Road Lahore., Lahore	i. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic ii. They have submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11) . iii. Their product is registered and being marketed since many years and no ADRs are reported till to date which establishes that product is safe and effective. iv. Hence, the said product may not be cancelled and show-cause may be revoked.

43.	Medisave Pharmaceuticals, Plot No.578-579 Sundar Industrial Estate Lahore., Lahore	i. In China, India and Bangladesh, diclofenac potassium is available in strengths above 50mg which covers half of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. ii. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. iii. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. iv. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. v. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). vi. Hence, the said product may not be cancelled and show-cause may be revoked.
44.	Harrison Pharmaceuticals, 10-Km Lahore Road Sargodha.	i. In China, India and Bangladesh, diclofenac potassium is available in strengths above 50mg which covers half of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. ii. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. iii. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. iv. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. v. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). vi. Hence, the said product may not be cancelled and show-cause may be revoked.
45.	FYNK Pharmaceuticals, 19-Km Ferozepur Road G.T. Road Kala shah Kaku Lahore	i. In China, India and Bangladesh, diclofenac potassium is available in strengths above 50mg which covers half of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. ii. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. iii. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. iv. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. v. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). vi. Hence, the said product may not be cancelled and show-cause may be revoked.
46.	Epharm Laboratories, A-40, Road No. 1, S.I.T.E. Super Highway Industrial Area, North Zone, Karachi	i. In China, India and Bangladesh, diclofenac potassium is available in strengths above 50mg which covers half of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. ii. In USFDA, the recommended daily dose is 50mg three times a day [up to 150mg daily for the treatment of pain and primary

		dysmenorrhea. In some patients an initial dose of 100mg followed by 50mg three times a day will provide better relief. iii. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. iv. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. v. They have also submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). vi. Hence, the said product may not be cancelled and show-cause may be revoked.

Annexure-D

Attendees who have filled Court cases			
Sr.No.	**Registration Holder**	**Statement/ Stance**	**Name & Designation of Representative (Attendees)**
1.	Paramount Pharmaceuticals, 36 Industrial Triangle, Kahuta Road Islamabad.	i. They are marketing their product since 1998 and this is favourite product of Physicians. This prescribing data shall be collected and shared with RRAs. i. The product may be marketed with a precautionary statement on its label regarding duration of use.	Mr. Nasir M. Qureshi CEO
2.	Siza International (Pvt) Ltd, 18 KM, Main Ferozepur Road, Lahore	i. Registered for 20 years and no ADRs are reported till now. ii. In response to question asked it was replied that no QPPV has been appointed. Safety efficacy data is not available with the firm. iii. No system is established regarding ADRs reporting. iv. No clinical trial data is available with the firm.	M. Saddiq Malik GM Regulatory Affairs
3.	Davis Pharmaceutical Laboratories, Plot No. 121 Industrial Triangle Kahuta Road Islamabad.	i. Main component is diclofenac in both formulations which is available in 75mg and 100mg in salt form of sodium. ii. In China, India, Egypt diclofenac potassium is available in strengths above 50mg which covers 38% of world population. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. iii. They have also consulted following RRAs regarding registration of Diclofenac potassium above 50mg and their responses are as under; a. Sweden: application for registration of said product is welcomed. b. Japan: They can register said product on the basis of Clinical Trials Data. c. Denmark: Formulation is not banned for registration due to any health and safety reasons. iv. In Martindale both salt forms of Diclofenac have same doses. v. In BNF recommended daily dose is 75-150mg in two to three divided doses and therefore both strengths 75mg and 100mg can fall under this dosage regimen. vi. Since, the product has not been proven either safe or unsafe, therefore the matter should be investigated on the basis of scientific grounds.	Mr. AmanULLAH Sheikh CEO

		vii. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic. viii. Hence, the said product may not be cancelled and show-cause may be revoked.	
4.	Quaper (Pvt) Ltd., 26-A S.I.E. Lahore Road Sargodha.	They agree with the decision of Registration Board for all registration holders.	Mr. Iftikhar Director
5.	Shrooq Pharmaceuticals (Pvt) Ltd, 21-Km Ferozepur Road, Lahore.	i. In 128th meeting of Authority it was decided to evaluate all the products, which are not available in RRAs, on the bases of safety and efficacy. ii. DRAP has sent emails to many RRAs for data regarding Diclofenac Potassium above 50mg but no RRAs has given any candid opinion declaring strengths above 50mg as unsafe. iii. Hence this product falls in grey area. iv. After reviewing, SmPC and Leaflets of reference products, DRAP has itself mentioned that clarity is required weather strengths above 50mg may be administered as single dose for longer period which further reiterates our point of view. v. Question was asked by member Registration Board regarding problem with administration of 200mg daily in divided doses of 50mg instead of 75 or 100mg then firm replied that in existing practice of prescribing it is not mentioned that drug should be administered after every 8 hours. vi. Thus, in order to maintain steady state level in line with the half-life of product it is more appropriate and safer to administer higher strengths.	Dr. Riaz Ahmed CEO

Non-Attendees who have filled Court cases

Sr.No.	Registration Holder	Written Response (if any)
6.	Pakheim International Pharma (Pvt) Ltd., 28 Km Ferozepur Road Lahore., Lahore	i. Our product Fen-K SR is a sustained release tablet and in our clinical trials on different volunteers we have found that ratio of diclofenac potassium in blood stream do not rise above 5.5 after 8 hours of ingestion which is within the normal range and safe. (Data of clinical trials will be submitted if desired). ii. Firm has also informed regarding following in-vitro release profile of their product which can be verified from dissolution study: 25-35% is released in first 2 hours. 35-45% is released in 2-4 hours. 45-55% is released in 4-6 hours. And NLT 80% is released after 10 hours. iii. We offer DRAP to conduct clinical trials from any DRAP recommended laboratory.

7.	Sapient Pharma, 123-S Industrial Area Kot Lakhpat Lahore., Lahore	-
8.	M/s. Cibex (Pvt) Ltd. F-405 S.I.T.E Karachi 000784	-

Case No.2. Personal Hearing Notices Issued to Registration Holders of Famotidine 10mg/5ml Liquid/Dry Suspension.

1. Registration Board, in its various meetings considered the case regarding *"Registration Status of Formulations (Diclofenac Potassium 75mg & 100mg and Famotidine 10mg/5ml) not approved by Reference Regulatory Authorities & Previous Decisions Taken by the Registration Board in its 250th & 258th Meeting"*.

2. With respect to Famotidine Suspension, complete record including proceedings & decisions of Registration Board and relevant decisions of DRAP's Authority have been reproduced as under:

Sr. No.	Formulation	Ref. Meeting No. of RB	Decision/Remarks
1.	Famotidine 10mg/5ml Suspension	M-250 *(held on 09th 10th July, 2015)*	***Remarks:*** ***Not approved by reference drug regulatory agencies. Internationally available formulation is dry powder for suspension in the strength of 40 mg/ 5 ml.*** ***(Ref: US FDA)*** **Decision:** i. Applicants shall revise their formulation as per innovator (new registration application with complete fee) within six months if manufacturing facility is approved by CLB. ii. For already registered drugs, same procedure as mentioned above (at Sr. No. i) shall be adopted. Otherwise show cause notice shall be issued for de-registration of registered drugs in this formulation. iii. All such application shall be processed on priority basis.

3. ***Decision taken by DRAP's Authority in its 70th meeting held on 05th Sep, 2019:***

For formulations containing "drugs" which were previously registered by the Registration Board and have proof of availability and prescription of last 10 years but are not available in the Reference Regulatory Authorities shall continue to be considered/ registered as drugs until and unless withdrawn on Safety, Efficacy and Quality reasons.

4. Decision of M-296 held on 08th-10th Sep, 2020:

Registration Board deliberated the case in the light of above stated facts / opinions and decided as under:

i. Since, all such formulations which are not approved by the Reference Regulatory Authorities; the safety and efficacy profile cannot be established in the absence of a well-established system for reporting of adverse events, so a reference shall be forwarded to DRAP's Authority with the request to review the decision taken in its 70th meeting held on 05-09-2019. In this regard, PE&R Division shall prepare a comprehensive document/agenda for consideration of Authority, keeping in view the practices adopted by RRA for all such formulations;

ii. For all those formulations which are registered/ applied in strengths, different from those approved by reference regulatory authorities, the registration holders/ applicants shall standardize their formulations (by submitting registration application with requisite fee, provided that the firm did not have same registration) in line with those approved by reference regulatory authorities. In this regard, recommendation shall be forwarded to DRAP's Authority to exempt all such cases/applications for standardization of formulation to be submitted on Form-5F/CTD format as notified vide SRO 713(I)/2018 dated 09-06-2018.

iii. Drug products withdrawn from RRA due to any commercial reason shall be considered for registration by Registration Board.

iv. Vitamin-mineral formulations will be considered as per vitamin policy approved by Policy Board and further adopted by Registration Board in its 295th meeting.

Keeping in view the point (i) and in order to proceed further for effective implementation/ execution of point (ii) to (iv) of the above-mentioned decision, the Authority was requested to review the decision taken vide its 70th meeting held on 05-09-2019.

5. Decision of DRAP Authority in its 125th meeting held on 03rd Nov, 2021:

The Authority deferred the agenda item for detailed deliberations keeping in view the therapeutic categories etc. of such formulations.

6. Proceedings of M-313:

i. The concept of reliance on the decisions of reference regulatory authorities adopted by the Registration Board in its 275th meeting was reiterated as deliberated during proceedings of 296th meeting with respect to instant case.
ii. Furthermore, Registration Board was apprised that a policy of reliance on reference regulatory authorities has also been approved by the Authority in its 73rd meeting held on 06-11-2019.
iii. Registration Board was also informed regarding court case (CP No.1545/2017) filed by M/s Cibex (Pvt.) Ltd., Karachi vs DRAP & others i.e, sub-judiced before the hon'ble Sindh High Court and written statement/updated registration status of such formulations on behalf of DRAP is required to be furnished.
iv. It was further deliberated that relevant registration holders/ manufacturers shall be provided with an opportunity to submit their response regarding (a) evidence for approval status of such formulation in reference regulatory authorities (b) product development data and relevant studies with respect to quality, safety and efficacy of these formulations.

7. Decision of M-313 held on 16th-18th Nov, 2021:

Keeping in view the detailed deliberations during proceedings of its 296th and 313th meeting, Registration Board decided as under:

i. To issue show cause notices to all registration holders/ manufacturers (including those listed in above tables) of below mentioned formulations under Section 7 (11)(d) of the Drug Act, 1976 that why the registration of their products may not be cancelled in the public interest. In this regard, the Board advised relevant registration sections to review the above-mentioned lists for correctness and issue notices accordingly. Moreover, any registration holder not included in above lists shall also be issued show cause notice after approval of Chairman Registration Board.
ii. Furthermore, management of these firms shall also be given the opportunity of personal hearing in the forthcoming meeting of the Board under section 42 of the Drugs Act, 1976.

S. No.	*Formulations*
1.	*Diclofenac Potassium Tablets/ Capsules in strengths greater than 50mg*
2.	*Famotidine Suspension in strength/dosage form other than 40mg/5ml Powder for Oral Suspension.*

iii. The Board also advised to share the updated status with hon'ble Sindh High Court if required.

8. Decision of 128th meeting of Authority held on 14th Dec, 2021:

I. The Authority endorsed the recommendations of Registration Board and made following decisions:-

A. Partially reviewed its earlier decision taken in its 70th meeting held on 05-09-2019, consolidated amended decision is reproduced as under:

1. For molecules falling in the grey areas or overlapping between PE&R and H&OTC division:

a. *Formulations/molecules already registered as "drugs" by Registration Board shall continue to be considered / registered as drugs irrespective of their status in Reference Regulatory Authorities until and unless withdrawn on Safety, Efficacy and Quality reasons.*

b. *If any such formulation was also enlisted by H&OTC Division, it will be un-enlisted. The applicants shall be advised to approach PE&R Division for processing of application for registration. For such un-enlisted applications, a separate queue shall be prepared by the PE&R Division in order to avoid discomfort to the applicants and assurance of availability of such formulations for patients.*

c. *This decision shall not apply to those formulations / molecules covered under Vitamin-Policy as approved by the Policy Board.*

2. *New formulations/molecules other than those which were already registered by Registration Board will be considered on the basis of their status in Reference Regulatory Authorities. If in the RRA, these are considered as drugs, these will be dealt by the PE&R Division while otherwise will be dealt by Health & OTC Division.*

3. *Endorsed the Reference Regulatory Authorities as adopted by the Registration Board from time to time and the criteria being opted to adopt RRAs. Registration Board was advised to issue a notification of adopted RRAs and comprehensive selection criteria for information and easy understanding of all relevant stakeholders.*

4. *Drug formulations/strengths which were previously registered by the Registration Board but are not available in any Reference Regulatory Authorities, shall be reviewed and disposed off keeping in view of safety and efficacy evidence / data in the Reference Regulatory Authorities.*

B. *Registration Board may decide and dispose off such formulations as and when identified/reported.*

II. *The Authority further advised Registration Board to review existing RRAs for veterinary drugs and submit its recommendations to the Authority for its consideration.*

9. In line with the decision taken by the Board in its 313th meeting, show-cause/personal hearing notices were issued to **162** registration holders for hearing before the Registration Board on 1st February, 2022 at 10 a.m. (for Diclofenac Potassium) & 2.30 p.m (for Famotidine). However, due to prevailing cases of COVID-19, personal hearings have been postponed (vide letter issued dated 27-01-2022).

10. <u>Current Status of CP No.1545/2017 filed by M/s Cibex in SHC [Famobex Suspension (Famotidine 10mg/5ml) Reg.No. 027108]</u>

M/s Cibex (Pvt.) Ltd., Karachi has also filed a court case against DRAP and others for issuance of letter [regarding change in registration status of Famobex Suspension (Famotidine 10mg/5ml; R#027108) from M/s Macter to M/s Cibex]. The last date of hearing was Friday, 28th January, 2022 wherein *"Syed Hakim Masood, Federal Inspector Drugs, DRAP, Karachi present and undertakes that the Petitioner's grievance including the other items will be considered in the forthcoming meeting which will probably be held on or about 01.02.2022. In the wake of above, the matter is adjourned to 04.03.2022."*

11. <u>Writ Petition No. 365/2022 filed by M/s Siza International Private Limited, Lahore [Ulcenil l0mg/5ml Suspension (Famotidine 10mg) Reg. No. 025568]:</u>

Operative part of court order dated 07-01-2022 is reproduced as under:

"Subject to notice in the meanwhile proceedings under the impugned show cause notice dated 29th of December, 2021 shall continue but the final decision shall not be made till the next date of hearing"

12. **Writ Petition No. 4168/2022 filed by M/s Shrooq Pharmaceuticals (Pvt) Ltd., Lahore [Fomen 10mg/5ml Suspension (Famotidine l0mg) Reg. No. 040312]:**

Operative part of court order dated 24-01-2022 is reproduced as under:

"At the outset learned proxy counsel submits that since identical matter (W.P. No. 365/2022) is pending adjudication before my learned brother Shahid Waheed. J. this petition be also referred to the said learned Bench.

In view of above, office is directed to place this petition before the said learned Bench after soliciting orders from the Hon'ble Chief Justice."

13. **Writ Petition No. 4409/2022 filed by M/s Pakistan Pharmaceuticals Products Pvt. Ltd., Karachi [Famdin Suspension (Famotidine 10mg) Reg. No. 055103]:**

Operative part of court order dated 28-01-2022 is reproduced as under:

"Subject to notice in the meanwhile proceedings under the impugned show cause notice dated 29th of December, 2021 shall continue but the final decision shall not be made till the next date of hearing"

14. **Writ Petition No. 24000/2022 filed by M/s Paramount Pharmaceuticals, Islamabad [Pepton 10 Suspension (Famotidine: 10mg) Reg. No. 033996]:**

Operative part of court order dated 21-04-2022 is reproduced as under:

"Subject to notice, in the meanwhile proceedings under the impugned show cause notice shall continue but the final decision shall not be made till the next date of hearing"

All the firms have challenged the Show Cause Notices issued for cancellation of their drugs stating violation of the decision taken in 70th Meeting of the DRAP Authority held on the 05-09-2019.

However, the decision taken in 70th Meeting of the DRAP Authority, has been reviewed in the 128th Meeting held on 14-12-2021, whereby Registration Board was allowed to review and dispose of registration of drugs keeping in view their safety and efficacy.

15. ***Decision of M-315 held on 01st Feb, 2022:***

Registration Board noted the information and advised to provide the opportunity of personal hearing in the next meeting of Registration Board.

16. In line with the decision of 315th meeting of Registration Board, following registration holders were issued show cause & personal hearing notices stating:

"Famotidine Suspension in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension has not been approved by any of the reference regulatory authorities (RRAs) adopted by the Registration Board in its 275th meeting and the safety & efficacy in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension are not established by any RRA. The above information provokes the provisions of Section 7 (l l)(d) and 42 of the Drugs Act, 1976. Accordingly, registration holders are required to show cause as to why the registration of their products may not be cancelled with immediate effect."

Famotidine **Date & Time of Hearing: 17th May, 2022 at 10:00 A.M.**			
Sr. No.	**Reg No**	**Brand Name & composition**	**Registration Holder**
1	58152	Trump 10mg/5ml Suspension Famotidine……..10 mg	M/s Adamjee Pharmaceuticals (Pvt.) Ltd., Plot 39, Sector 15, Korangi Industrial Area, Karachi.
2	35275	Ge Pep Suspension Each 5ml contains:- Famotidine 10mg	Akson Pharmaceuticals Co. (Pvt.) Ltd.
3	78725	Al-Famot Oral Liquid Suspension 60ml Famotidine …… 10mg	Ali Industries, Plot No.239/C Sundar Industrial Estate Raiwind Road Lahore.,

4	54717	Afomit Susp Famotidine ……..10mg	M/s Alliance Pharmaceuticals (Pvt) Ltd, Plot # 112-A, Hayatabad, Industrial Estate,Peshawar.
5	43409	Sypep Suspension Famotidine……10 mg	M/s. Alson Pharmaceutical, 169, Road No. 7-B, Industrial Estate Hayatabad, Peshawar.
6	40816	Fambria Suspension Famotidine... 10mg	Ambrosia Pharmaceuticals,, Plot No.18, St. No.9, National Industrial Zone, Rawat, Islamabad.,
7	60333	Famodex Suspension Famotidine …… 10mg	Ameer Pharma (Pvt) Ltd, , 23-KM, Sheikhupura Road,Lahore.,
8	47354	Zebid Suspension Famotidine……10mg	M/s Atco Laboratories Ltd, B-18, S.I.T.E, Karachi.
9	77070	Feptid Oral Suspension Famotidine: 10mg	Axis Pharmaceuticals , 3-B Value Addition City 1.5 Km Khurrianwala – Sahanwala Road Faisalabad
10	24255	Acicon Suspension Each 5ml contains:- Famotidine USP…..10mg	M/s Barrett Hodgson Pakistan (Pvt) Ltd., F/423, S.I.T.E., Karachi.
11	70711	Acicon 10mg/5ml Dry Suspension Famotidine …….10 mg	M/s Barrett Hodgson Pakistan (Pvt) Ltd., F/423, S.I.T.E., Karachi.
12	25469	Kamcid Suspension Each 5Ml Contains:- Famotidine.....10mg	M/s Bloom Pharmaceuticals Pvt. Ltd, Plot # 30, Phase I & II, Industrial Estate, Hattar.
13	30082	Nulcer Suspension Famotidine …….10mg	M/s. Brookes Pharma (Pvt) Ltd., Plot No. 58-59, Sector No. 15, Korangi Industrial Area,Karachi.
14	69070	Femcare Suspension Famotidine ……10mg	Care Pharmaceuticals, 8-KM Thokar, Raiwind Road, Lahore.,
15	45470	Pharmotidin Suspension Famotidine. …….. 10 mg	M/s. E-Pharm Laboratories, A-40 S.I.T.E Super Highway North Karachi, Karachi.
16	59498	Fedcid Suspension Each 5ml contains:- Famotidine 10mg	M/s Fedro Pharmaceutical Labs (Pvt) Ltd., 149-Industrial Estate, Jamrud Road, Hayatabad.
17	46936	H2foz Suspension Famotidine ……..10mg	M/s Fozan Pharmaceutical Industrial (Pvt) Ltd., 36- A, Industrial Estate, Hayatabad, Peshawar
18	62698	NO-UL Suspension Famotidine ……10mg	Fynk Pharmaceuticals,, 19 K.M. G.T. Road, Kala Shah Kaku, Lahore.,
19	25149	Fadiphine Suspension Each 5ml contains Famotidine.....10mg	Global Pharmaceuticals, Plot No 204-205, Kahuta Triangle, Industrial Area, Islamabad
20	33340	Fagastril Syrup Famotidine…….10mg	Gray's Pharma, Islamabd,
21	75050	Dinex Suspension Each 5 ml contians:- Famotidine … 10 mg	Gulf Pharmaceuticals, Plot No.4, St.No.S-6, National Industrial Zone, Rawat,
22	59947	Gaster Suspension Famotidin ……. 10mg	Hamaz Pharmaceuticals (Pvt) Ltd,, 22 Km Lutafabad Road, Multan.,

23	59885	Gestrodine Suspension Each 5ml contains:- Famotidine…….10mg	Harmann Pharmaceutical Labs (Pvt) Ltd,, 16 -Km Multan Road,Lahore.,
24	30273	Cantil Suspension Famotidine……10mg	Helicon Pharmaceutek, Pakistan (Pvt) Ltd,, Model Town Road, Faisalabad,
25	31233	Peprid Suspension Famotidine …….10mg	M/s. Helix Pharma Pvt. Ltd., A-56, Manghopir Road S.I.T.E., Karachi.
26	41472	Hifame Suspension Famotidine …… 10mg	M/s Hicon Pharmaceuticals. 131-Industrial Estate, Hayatabad Peshawar.
27	47829	Famonil Suspension 60ml Famotidine……..10mg	M/s. Hisun Pharmaceutical Industry, 37-A R-02 Industrial Estate Gadoon Amazai, District Swabi.
28	54455	Famosib Suspnesion Famotidine 10mg	Irza Pharma (Pvt) Ltd, 10/2 Km Sheikhupura Road, P.O. Kot Abdul Malik, Sheikhupura.
29	54287	Stomachcare Susp Each 5ml contains:- Famotidine 10mg	Jawa Pharmaceuticals (Pvt.) Ltd.,
30	61758	Kohiton Suspension Famotidine……..10mg	M/s. Kohs Pharmaceuticals (Pvt) Ltd., Plot No. P/8 S.I.T.E, Hyderabad.
31	71168	Famotidine 10mg/5ml Suspension Famotidine …… 10mg	Lawrence Pharma (Pvt.) Ltd, , 10.5Km Sheikhupura Road, Lahore.,
32	54223	Myolif Suspension Famotidine……..10mg	Life Pharmaceutical Company, 24-III, Industrial Estate, Multan
33	56653	Nogacid Suspension Famotidine…….10mg	M/s Lowitt Pharma (Pvt) Ltd.,Plot No.24-Industrial Estate, Hayatabad, Peshawar.
34	58116	Atodine Suspension 10mg/5ml Famotidine ……..10 mg	M/s Macquin's International, F-2/H, PTC Industrial Complex S.I.T.E, Karachi.
35	27108	Famobex Suspension Each 5Ml Contains:- Famotidine…..10.000mg	M/s Macter International Limited. F-216, S.I.T.E, Karachi.
36	63004	Famoday Suspension Each 5ml contains:- Famotidine 10mg	Max Pharmaceuticals, Rawalpindi
37	27115	Famorex Suspension Each 5Ml Contains:- Famotidine……..10mg	Mediceena Pharma (Pvt) Ltd, , 27- K.M, Raiwind Road, Lahore
38	63081	Pepcimed Suspension 10mg/5ml Famotidine…….10mg	M/s. Medicraft Pharmaceuticals (Pvt.) Ltd.,126-B Industrial Estate Hayatabad, Peshawar.
39	33684	Acidrol Suspension Famotidine ……10mg	Medisearch Pharmacal, Lahore.
40	54613	Efdine Suspension Famotidine……..10mg	M/s. Meditech Pharmaceuticals, 15-D Industrial Estate, Jamrud Road, Peshawar,
41	59540	Motidin Suspension Famotidine….10mg	Medley Pharmaceutical,, 41-A P.S.I.E Jhang Bahtar Road, Wah Cantt,

42	75259	Modin Suspension Famotidine: 10mg	Metro Pharmaceuticals, Plot No. 14 St. No. SS-2 National Industrial Zone (RCCI) Rawat Islamabad, Islamabad
43	66298	Maripep Each 5ml contains:- Famotidine.. 10mg	Miracle Pharmaceuticals (Pvt.) Ltd., Islamabad,
44	33704	Neofam Suspension Famotidine……..10mg	Neomedix , Plot No.5, N-5 National Industrial Zone Rawat (Islamabad), ,
45	38876	Neutidin Suspension 10mg/5ml Famotidine…….10mg	Neutro Pharma (Pvt) Ltd, 9.5Km,SheikhupuraLahore,
46	31646	Capcid Suspension Famotidine…….10mg	Olive Laboratories,, Plot # 52-S6, National Industrial Zone ,
47	77441	Famonyx 10 Suspension Famotidine: 10mg	M/s. Onyx Pharmaceuticals Industries, 30-A Industrial Estate Mansehra.
48	55103	Famdin Suspension Famotidine……10mg	M/s Pakistan Pharmaceutical Products (Pvt) Ltd., D-122, Sindh Industrial Trading Estate, Karachi.
49	33996	Pepton Suspension Famotidine…..10mg	Paramount Pharma,Islamabad, 36,Industrial Triangle Kahuta Road, Islamabad,
50	25565	Reducid Suspension Famotidine.....10mg	M/s Platinum Pharmaceuticals (Pvt) limited, A-20 North Western Industrial Zone, Bin Qasim, Karachi
51	41619	Servipep Susp. Famotidine…….10mg	M/s. Polyfine Chempharma, 51 Industrial Estate, Hayatabad, Peshawar.
52	41444	Famo Rains Suspension Famotidine ……10 mg	Previous Address: Mac & Rains Pharmaceuticals (Pvt) Ltd, 1.5 KM, Manga Raiwind Road, Manga Mandi, Lahore. Current Address: M/s Searle IV Solutions (Pvt) Ltd, 1.5 KM, Manga Raiwind Road, Manga Mandi, Lahore.
53	52452	Fam-PH Suspension. Famotidine……..10mg	Previous Address: Evergreen Pharmaceuticals (Pvt) Ltd, Plot No. 590, Sundar Industrial Estate, Lahore. Current Address: M/s Allmed (Pvt) Ltd, Plot No. 590 Sundar Industrial Estate, Lahore
54	64891	Famoprime Suspension 10mg Famotidine ……10mg	Prime Labs (Pvt) Ltd, 9.5 Km Sheikhupura Road, Lahore.,
55	27550	Loacid Suspension 10mg/5ml Famotidine …… 10mg	Raazee Therapeutics (Pvt) Ltd., 48-Km Lahore Kasur Road Kasur., Kasur, , Pakistan
56	69396	Famtac Suspension Famotidine…10mg	Rasco Pharma,, 5.5 KM Raiwind Road Ali Razabad, Lahore,
57	30124	Recid Syp Famotidine…..10mg	M/s. Regent Laboratories C-20, S.I.T.E Super Highway, Karachi

58	64293	S.Famers 10mg Syrup Famotidine……..10mg	M/s Sayyed Pharmaceutical (Pvt) Ltd.,Plot No. 67/2, Phase 3, Industrial Estate, Hattar. Haripur.
59	28254	Famoscot Oral Suspension 10mg Famotidine……10 mg	Scotmann Pharmaceuticals, 5D, I-10/3 Industrial Area, Islamabad
60	55282	Almadine Suspension 10mg/5ml Famotidine…10mg	Selomore Pharmaceuticals (Pvt) Ltd.,35 KM, Multan Raod, lahore
61	25952	Famoat Suspension 10mg/5ml Famotidine …… 10mg	Shaigan Pharmaceutical (Pvt) Ltd., 14-Km Adyala Road Post Office Dahgal Rawalpindi, Rawalpindi, , Pakistan
62	40312	Fomen Suspension 10mg Famotidine…..10mg	Shrooq Pharmaceutical (Pvt) Ltd, 21-KM, Feroze Pur Road, Lahore
63	25568	Ulcenil Suspneion Each 5Ml Contains:- Famotidine....10mg	Siza International (Pvt) Ltd, 18 KM, Main Ferozepur Road, Lahore
64	34789	Gastridine Suspension Famotidine……..10mg	M/s T.G. Pharma, E-30 Sector 15, Korangi Industrial Area, Karachi. [Previous Title: M/s. Unicorn Pharma] Karachi
65	65555	Therafame Suspension 10mg/5ml Famotidine…..10mg	Theramed Pharmaceutical, , 331-J-1 Johar Town Lahore,
66	42764	Fastine Suspension Famotidine ……..10mg	Trigon Pharmaceutical (Pvt) Limited, 18 Km Raiwind Road, Lahore
67	67940	Gdicd Suspension Famotidine…10mg	Unison Chemical Works, Lahore,
68	25037	Peptiban Suspension Each 5ml contains Famotidine.....10mg	Werrick Pharmaceuticals, 216-217, I-10/3, Industrial Area, Islamabad.,
69	65677	Famid 10mg Suspension Famotidine……10mg	Wilshire Laboratories,, 124/A, Kotlakhpat, Indus. Area, Township Scheme, Lahore.,
70	65956	Famotop Suspension Famotidine…….10mg	Xenon Pharma, Lahore.
71	57740	Famtaza Dry Suspension Famotidine…..…….....10mg	M/s. Zafa Pharmaceutical Laboratories (Pvt.) Ltd., L-1/B Block 22 Federal B Industrial Area, Karachi
72	61150	Flut Suspension Famotidine……..……10mg	M/s Zephyr Pharmatec (Pvt.) Ltd, A-39, SITE II, Super Highway, Karachi
73	43731	Ulcare.Suspension.10mg. Famotidine……10mg	M/s. Z-Jans Pharmaceuticals (Pvt) Ltd., 148-A, Industrial Estate Hayatabad, Peshawar.
74	038876	Neutidin Suspension 10mg/5ml Famotidine……10mg	Neutro Pharma (Pvt) Ltd, 9.5Km,Sheikhupura Lahore.
75	044794	Famofit Suspension 10mg/5ml Famotidine……10mg	Synchro Pharmaceuticals, 77-Industrial Estate Kot Lakhpat Lahore.

21. It is also pertinent to mention here that subsequent to the decision of 250th meeting of Registration Board regarding "Famotidine Suspension", following registration holders applied for revision of their registered/approved products in line with the reference product approved by RRA:

S/N	Reg Holder	Previously Approved/ Registered formulation	Revised formulation
1.	M/s. Bryon Pharmaceuticals (Pvt) Ltd., 48 Hayatabad Industrial Estate Peshawar.	Nocer 10 suspension Each 5ml contains: Famotidine...10mg (R#042966)	Nocer 40 Dry Suspension Each 5ml contains: Famotidine…….40mg (R#087998)
2.	M/s Astellas Pharmaceutical (Pvt) Ltd. Industrial Estate, Hayatabad, Peshawar.	Famos Dry Suspension 10mg/5ml Each 5ml contains: Famotidine…10mg (Approved in M-272, Reg. letter not issued)	Famallas Dry Suspension 40mg/5ml Each 5ml contains: Famotidine……40mg (R#108745)
3.	M/s Pharmix Laboratories (Pvt) Ltd. 21-Km Ferozepur Road Lahore	Ulcofin Suspension 10mg Each 5ml contains: Famotidine……..10mg (USP Specification) (R#053752)	Ulcofin Dry Powder Suspension 40mg/5ml Each 5ml contains: Famotidine……..40mg (R&I date: 29-11-2022, Fee of Rs.20000/-) (Under process of evaluation)

22. Furthermore, following responses have been received against the show cause notices:

S.NO	COMPANY NAME	RESPONSE
1.	**M/s Helicon Pharmaceutiek Pakistan (Pvt) Ltd**	Reference to your letter no. F.5-6/2021-Reg-11 (M-313)(Misc) dated 29th December 2021 & F.5-3/2022-Reg-11 (M-317)(Misc) dated 06th April, 2022. This drug was registered on 09.08.2003. Thus has a prescriber doctor's confidence in the brand. It is very long procedure for new registration. Whereas we also have been granted Cantil 40mg tablet (Famotidine) under registration no. 016854. The patients who could not take tablet and have to choose take suspension according to the doctor's prescription. Therefore in the interest of patients and prescribing doctors we request for substituting the formulation from 10mg/5ml to 40mg/5ml in suspension form. Necessary approvals may kindly be granted for complying with the decision of Registration Board in peculiar circumstances of our case of change of strength of our registered formulation namely Cantil Suspension registration no. 030273 from 10mg/5ml to 40mg/5ml. We follow the SOP's in this regard.
2.	**M/s Lotus Pahrmaceuticals (Pvt) Ltd, Islamabad**	With reference to your letter No F.5-6/2021-Reg-II (M-313) (Misc) dated 29th December 2021, it is stated that we are not manufacturing Famotidine 10mg/5ml (Pepdine Syrup) since Oct-2019.

		Furthermore, we have no intention to manufacture above mentioned product in future.	
3.	**M/s Adamjee Pharaceuticals Pvt Ltd**	With reference to your letter No.F.3-2/2022-Reg-I (M-317)(Misc) dated 06th April, 2022 we have no objection to cancellation of Trump 10mg/5ml Suspension. Please cancel the said products after complete utilization of the packaging materials of the said products.	We reference to your letter No. F 3-6/2021-Reg -1 (M-313) Misc. dated 7th January 2022, we have no objection to cancellation of trump 10mg/5ml Suspension We will utilize our raw Material to manufacture Trump 40mg and 20mg tablets (Famotidine 40mg and 20mg) Registration No. 58151 and 58150 respectively,
4.	**M/s Sayyed Pharmaceuticals (Pvt.) Ltd, Hattar,**	Reference to your letter no. F 3-6/2021-Reg-1 (M-313 (Mis) dated 29th December, 2021, regarding cancellation of registration of S-Famers 10mg Syrup (Famotidine 10mg /5ml) registration no. 064293, we M/s Sayyed Pharmaceuticals (Pvt) Ltd, 67/2, Phase 3 Industrial Estate, Haripur hereby submit that, In Martindale 38th edition volume 2, Page 1842 famotidine is licensed for use in children in some countries, including the USA, It is used to inhibit gastric acid secretion and may be given orally in the management of gastro esophageal reflux disease, the following initial oral doses of famotidine are suggested, according to age, Under 3 month: 500 micrograms/kg once daily. 3 month up to year: 500 microgram/kg twice daily. 1-16 Years: 500 micrograms/kg twice daily up to 40mg twice daily may also be given. In the management of peptic ulcers, famotidine may be given to children from 1 to 16 years in an initial oral dose of 500 micrograms/kg daily either in a single dose at night or in 2 divided doses However we will apply to change our drug product from S-famers 10mg Syrup (Famotidine 10mg/5ml) Reg No. 064293 to famotidine 40mg 5ml dry powder for Suspension as per decision of the honorable registration board.	
5.	**M/s Macquin's International Karachi**	Kindly refer to your letter No. F 3-6/2021-Reg-1 (M-313) Misc date 29 December 2021, the above subject, it is respectfully submitted that our CEO is suffering from Covid 19 he will be available as per doctor Prescription in mid-February,	

		It is therefore humble requested he may please be allowed to appear before the Registration Board for Personal hearing by 10 February 2022. We shall be remain grateful in anticipation for granted us one month time on medical ground.

Proceedings During 317th Meeting:

1. The instant proceedings have been undertaken in pursuance of decision taken by the Registration Board in its 313th Meeting wherein Show Cause Notices were issued to all registration holders of Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension *viz.* Famotidine 10mg/5ml and 40mg/5ml Liquid Suspension under Section 7(11)(d) of the Drugs Act, 1976 for cancellation or suspension of registration of the aforementioned registered drug products in the public interest. The Show Caused registration holders of the drug in question were also issued personal hearing notices under Section 42 of the Drugs Act, 1976 and were heard at length.

2. A list of pharmaceutical companies which did not attend the meeting is at Annexure-A; a list of pharmaceutical manufacturers who have shown satisfaction on instant proceedings undertaken by the Registration Board, without raising any challenge to the show cause notice and consented to accepting the decision of the Registration Board is at Annexure-B; a list of pharmaceutical companies who either attended personal hearing or responded through written arguments is at Annexure-C; a list of pharmaceutical companies who have filed Writ Petitions before the Hon'ble Lahore High Court, Lahore is at Annexure-D.

3. For the sake of brevity and to avoid repetition, all arguments advanced by the registration holders are amalgamated. The arguments raised in brief in replies to the notice as well as during personal hearing were that the Board in its 313th Meeting without conducting any proper fact finding enquiry decided to issue show cause notices by disregarding that many registrations of the drug had subsisted for more than a decade without any reported adverse effects; similarly, the show cause notice and personal hearing notices were also devoid of reasons and hence the same are *void ab initio*. The Board had granted registration of drug after satisfying itself of its safety and efficacy and cannot now take a somersault. Non-registration or unavailability of a drug in Reference Regulatory Authorities is an irrational ground for questioning the safety and efficacy of drugs since these have proved effective in the domestic market for years; furthermore, the aforementioned ground is alien to the drug laws and cannot be invoked for any regulatory action. Lastly, it was argued that discontinuation of the drug would adversely affect the patients along with incurring immense financial loss upon the registration holders.

4. Record has been perused with the able assistance of the representatives of the registration holders and arguments have been heard. Since common questions of law and facts are involved, therefore, all notices are decided through a common order.

5. Succinctly stated the facts of the matter are that the Registration Board in its various meetings considered the cases of, *inter alia*, Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension i.e. the drugs in question. It was concluded that from the available record and reviewing of information available from the Reference Regulatory Authorities ('**RRAs**') that no data regarding efficacy of Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension is available, so continuity of the formulations was not considered justifiable. With regards to the drug in question, decision has already been taken in the 250th Meeting of the Board dated 09th and 10th of July, 2015, which is reproduced as hereunder:

> "**Decision:**
> i. Applicants shall revise their formulation as per innovator (new registration application with complete fee) within six months if manufacturing facility is approved by CLB.
> ii. For already registered drugs, same procedure as mentioned above (at Sr. No. i) shall be adopted. Otherwise show cause notice shall be issued for de-registration of registered drugs in this formulation.
> iii. All such application shall be processed on priority basis.".

6. In the meanwhile, DRAP Authority in its 70th Meeting held on 05-09-2019 decided the following:

> *"For formulations containing "drugs" which were previously registered by the Registration Board and have proof of availability and prescription of last 10 years but are not available in the Reference Regulatory Authorities shall continue to be considered/ registered as drugs until and unless withdrawn on Safety, Efficacy and Quality reasons."*

7. Subsequently, Registration Board in its 296th Meeting held on the 8th-10th September, 2020, decided to request the DRAP Authority to review its above mentioned decision in the following words:

> *"Since, all such formulations which are not approved by the Reference Regulatory Authorities; the safety and efficacy profile cannot be established in the absence of a well-established system for reporting of adverse events, so a reference shall be forwarded to DRAP's Authority with the request to review the decision taken in its 70th meeting held on 05-09-2019. In this regard, PE&R Division shall prepare a comprehensive document/agenda for consideration of Authority, keeping in view the practices adopted by RRA for all such formulations;"*

8. The DRAP Authority in its 128th Meeting held on 14-12-2021 was pleased to accept the request the Registration Board and reviewed its 70th Minutes in the following words:

The Authority endorsed the recommendation of Registration Board and made following decisions:-

A. Partially reviewed its earlier decision taken in its 70th meeting held on 05-09-019, consolidated amended decision is reproduced as under:

[…]

4. Drug formulations/ strengths which are previously registered by the Registration Board but are not available in any Reference Regulatory Authorities, shall be reviewed and disposed of keeping in view of safety and efficacy evidence/ data in the reference Regulatory Authorities."

9. In pursuance of the above mentioned, Registration Board in 313th Meeting decided to issue Show Cause Notice to the Petitioner and other pharmaceutical concerns to all registration holders of Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension under Section 7(11)(d) of the Drugs Act, 1976 for cancellation or suspension of registration of the aforementioned in the public interest. Therefore, in pursuance of the decision by the DRAP Authority taken in its 128th Meeting, the instant proceedings are being undertaken.

10. It is to be noted at the outset that registration or licensing has been held by the Superior Courts to be a privilege not a right which can always be cancelled or suspended in accordance with the law. It has argued at length that the Registration Board granted registration after determining safety, efficacy and quality of drugs which was renewed over time, therefore, the Board cannot after passing of many years re-assess the safety, efficacy and quality of drugs. The argument is fallacious as Rule 27 of the Drugs (Licensing, Registration and Licensing) Rules, 1976 ('**Rules, 1976**') while providing the duration of drug registration also added that the registration can always be cancelled or suspended earlier as well. The grounds on which the drug registration can be suspended or cancelled are provided in Section 7 (11) of the Drugs Act, 1976, and therefore, the argument that registration once granted will continue in perpetuity is against the law. Furthermore, Section 21 of the General Clauses Act, 1897, grants the Board the power to rescind any drug registration in accordance with the grounds provided in Section 7 (11) of the Drugs Act, 1976. The argument in discussion is also fallacious for the reason that scientific pharmaceutical knowledge is always in the process of evolution and decision based on knowledge available at one point of time cannot be used to defeat the just and fair decision to be taken in future with the broadening of knowledge. This principle has been encapsulated in Rule 30 (12) of the Rules, 1976, which grants the Board power to seek any information at any point in time post-registration regarding the safety, efficacy and quality of drugs. The Board has ample powers under Rule 30 (2) to rescind, vary or modify any decision taken by it in the larger public interest to perform its statutory regulatory duty of ensuring the provision of safe and efficacious drugs and medicines to the public at large.

11. The primary ground which has prevailed with the Board for initiating the instant proceedings is that the drug in question (Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension) is neither approved by any of RRAs nor any data regarding its efficacy is available. To better appreciate the argument, it is important to understand the scheme of the law which allows for placing reliance on RRAs as well as its importance for performing the statutory regulatory duties.

12. Applicant companies are generic drug product manufacturers. The generic drug product is pharmaceutically equivalent to the innovator's drug product as it contains the identical medicinal ingredients in the same amount/strength and dosage form and it must have same pharmacokinetics, pharmacodynamics, indications, contraindications, side effects etc. A generic drug product must work in the same way as that of innovator's drug product and, therefore, it can be interchanged with the innovator's drug product. Famotidine Liquid Suspension has no innovator and applicant companies have neither conducted nor provided any efficacy study to establish the aforementioned points (i.e., pharmacokinetics, pharmacodynamics, indications, contraindications, side effects etc.).

13. Criteria for grant of registration of any drug product is safety, efficacy and quality parameters and the onus for provision of relevant data to establish aforementioned parameters under the applicable law is upon the applicant/registration holder. For this purpose, applicant either needs to provide sufficient data to satisfy the aforementioned parameters by themselves, or provide reference to approval of registration granted by any Reference Regulatory Authorities ('**RRAs**'); this serves the purpose for determining safety and efficacy of the drugs. RRAs are regulatory authorities of developed countries which have stringent regulatory regimen and have developed robust mechanisms for determining drug safety, efficacy and quality and their decisions are supported by the rapid advances in sciences as well as empirical studies. Even WHO supports the reliance by developing countries on decisions of the Stringent Regulatory Authorities to ensure availability of quality assured, safe and effective health products and to avoid redundancy, global harmonization of standards and wastage of limited regulatory and financial resources. This reliance enables Registration Board and DRAP to have evidence for robust, accurate and evidence based decision-making, considering that the products registered and sold in the countries of RRAs have already been strenuously evaluated to fulfil the harmonized standards of safety, efficacy and quality as adopted by WHO, ICH, etc. This reliance also enables DRAP being the national regulatory authority in undertaking post marketing surveillance, particularly of matters related to safety and efficacy of drug. RRAs have stronger reporting and information sharing system, which can be used by DRAP as a

national regulatory authority as a useful tool for surveillance, new available treatments and new indications or contra-indications.

14. It is pertinent to mention that since adoption of RRA, DRAP has approved only those drug products which are either approved by RRAs based on their safety and efficacy assessment or after provision by the applicant pharmaceutical concern of relevant data regarding their safety, efficacy and quality. Moreover, DRAP has also started review process of already registered drugs to ensure availability of quality assured safe and effective therapeutic goods to ailing patients in the larger public interest.

15. The Registration Board in accordance with the global best practices, in its 275th Meeting held on 25th to 27th of October, 2017, decided to adopt the RRAs and their decisions "as reference for molecules/ formulations as reference for molecules/ formulations (in same dosage form and strengths) along with clinical trials for human purpose"; this decision was also upheld by the DRAP Authority in its 128th meeting. The aforementioned decision has since been applied by the Registration Board and also been followed by all pharmaceutical concerns for registration of their products without any caveat. Currently, all registered formulations and dosage of drugs and medicines in Pakistan are now required to comply with the details/ specifications as approved by RRAs or provide sufficient data for assessing safety, efficacy and quality of the drug product. Aforementioned decision has been taken to ensure availability of quality assured safe and effective medicines to ailing patients as it is matter of prime public health concern.

16. The adoption of RRAs allows the performance of the statutory duty to "adopt […] standards and guidelines to ensure safety, efficacy, and quality of therapeutic goods" as ordained under Section 7 (t) of the DRAP Act, 2012. Therefore, the DRAP Authority *[created under Section 2 (iv) and Section 7 of the DRAP Act, 2012]* also approved the policy of reliance on RRAs in its 73rd Meeting held on 06-11-2019. Hence, the argument that reliance on RRAs is alien to the drug laws and without any basis for determining safety and efficacy of drugs is baseless. Furthermore, as all pharmaceutical concerns are effectively complying with decision by the Board regarding reliance on RRAs in approval of their drug products and have never raised any objection or caveat to it, therefore, they are restrained and estopped by their own conduct from challenging it in the instant proceedings.

17. As the legality of reliance on RRAs has been detailed above, the Board has undertaken a thorough inquiry of the registration and availability of Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension in RRAs. It was found that famotidine is registered only in the form of Dry Suspension with strength of 40mg/5ml. There is no

evidence of approval of Famotidine liquid suspension in strengths of 10mg/5ml and 40mg/5ml in RRAs.

18. *It is to be noted that data regarding efficacy of famotidine liquid suspension with strength of 10mg/5ml and 40mg/5ml has not been provided by the registration holders as under the law i.e.* Rule 30 (12) of the Rules, 1976, *the burden of proof is upon the person seeking to continue registration to advance data regarding the safety and efficacy of the drugs. It has been argued that the said drug has been freely available in the domestic market for years without any adverse effect being reported, which is proof enough of its safety and efficacy. However, no applicant can share any authentic clinical data regarding efficacy of famotidine liquid suspension with strength of 10mg/5ml and 40mg/5ml in their company rather argued that till data no adverse event has been reported after use of these formulations and argued that the absence of such data serve as an evidence for drug's safety and efficacy.*

18. *It is also to be noted that pharmacovigilance data or even stability studies data is not the substitute of positive data regarding the efficacy of drugs which has been universally accepted to arise only from valid clinical trials to be performed in accordance with the Bio-Study Rules, 2017.* In light of the above discussed, allowing the registration of Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension to continue shall not be in the public interest as statutory intent of enacting the drug laws is the provision of safe and efficacious drugs and medicines to the people at large without any compromise. The task of the regulator is to curb any potential future menace from advent of sub-therapeutic use of drug and thus adversely affecting the public at large rather than responding belatedly to public health crisis which could have been mitigated by applying the pre-cautionary principle.
19. The Board noted that regulatory action was being taken only against registration of Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension for lack of its efficacy data; all pharmaceutical concerns were still free to obtain registration of Famotidine 40mg/5ml Powder for Oral Suspension after completion of legal formalities. Therefore, the registration holders can still maintain the market share of their respective brand of the drug in question and hence, bear no financial or reputational loss. This observation was posed to all the registration holders during personal hearings, but no satisfactory reply was given by them for their insistence on maintaining registration of Famotidine in strength/ dosage form other than 40mg/5ml Powder for Oral Suspension which lacks data regarding its efficacy, rather than accepting registration of Famotidine 40mg/5ml Powder for Oral Suspension which is both safe and efficacious and also serves the same

medical use. This will preserve them from any financial loss as they can serve the patients in dosage forms with evidence based efficacy profile of drug product.

20. It was argued by the representative of M/s Scotmann, Islamabad that Famotidine 10mg is approved in dispersible tablet dosage form in USFDA and is safe in patients with compromised renal clearance. Secondly, in patients with renal impairment, USFDA recommends dosage regimen of *"20mg every other day"* or an alternate regimen of "*10 mg once daily (Since 20 mg or 40 mg tablet strength cannot be used for this dosage regimen, use an alternate famotidine formulation)".* However, above recommendation is specific for patients of renal impairment. Furthermore, alternate famotidine formulation may not necessarily be 'famotidine 10mg/5ml suspension' as 'famotidine 10mg chewable tablet' is also approved by USFDA. It was also contended that dose adjustment is easy in 10mg/5ml as compared to 40mg/5ml. However, in response to a question raised by Registration Board it was responded that neither any approval has been granted by RRA which supports that both 10mg Tablet and liquid Suspension have same efficacy profile nor any document confirming efficacy of 10mg/5ml suspension is available with them for sharing with Registration Board.

21. Director DTL Karachi dissented with the decision taken by the Board and opined not to suspend registration of these products.

Decision:

In light of the foregoing discussions, risk-benefit analysis and public health impact of Famotidine 10mg/5ml and 40mg/5ml, the Board made following decisions:

i. Suspended all drug registrations of Famotidine 10mg/5ml and 40mg/5ml Liquid Suspension under Section 7(11)(d) read with Section 42 of the Drugs Act, 1976 in the larger public interest, with immediate effect as neither approved by any Reference Regulatory Authorities nor efficacy data is available with any registration holder. Period of suspension will be for one (01) year or till demonstration of efficacy by conducting indigenous clinical trials in accordance with Bio Study Rules, 2017 or approval by Reference Regulatory Authorities whichever is earlier. After provision of aforementioned data, cases of such pharmaceutical firms shall be considered on merit by the Registration Board

ii. Suspended manufacturing and import of these drug products immediately and directed to withdraw available stocks from the market in the larger public interest. QA&LT Division, DRAP will monitor and implement the decision in coordination with the respective provincial governments.

iii. Final decision regarding pharmaceutical concerns who have obtained interim relief from the Hon'ble Lahore High Court, Lahore shall be announced after decision and direction by the Hon'ble Court. Legal Affairs Division is requested to place the instant decision before the Hon'ble Court and seek expeditious disposal of the matter in the larger public interest.

iv. Recommended DRAP Authority for out of queue consideration of registration applications of Famotidine 40mg/5ml Dry Suspension in order to facilitate the registration holders affected by the instant decision.

Annexure-A

Non-Attendees	
S. No.	**Registration Holder**
1.	Ali Industries, Plot No.239/C Sundar Industrial Estate Raiwind Road Lahore.,
2.	M/s Alliance Pharmaceuticals (Pvt) Ltd, Plot # 112-A, Hayatabad, Industrial Estate, Peshawar.
3.	M/s. Alson Pharmaceutical, 169, Road No. 7-B, Industrial Estate Hayatabad, Peshawar.
4.	Ameer Pharma (Pvt) Ltd, 23-KM, Sheikhupura Road,Lahore.,
5.	Axis Pharmaceuticals, 3-B Value Addition City 1.5 Km Khurrianwala – Sahanwala Road Faisalabad
6.	Care Pharmaceuticals, 8-KM Thokar, Raiwind Road, Lahore.
7.	M/s. E-Pharm Laboratories, A-40 S.I.T.E Super Highway North Karachi, Karachi.
8.	M/s Fedro Pharmaceutical Labs (Pvt) Ltd., 149-Industrial Estate, Jamrud Road, Hayatabad.
9.	M/s Fozan Pharmaceutical Industrial (Pvt) Ltd., 36- A, Industrial Estate, Hayatabad, Peshawar
10.	Fynk Pharmaceuticals, 19 K.M. G.T. Road, Kala Shah Kaku, Lahore.,
11.	Gray's Pharmaceuticals Plot No.02 Street No 03 National Industrial Zone, Rawat Islamabad (Previous Address: Gray's Pharmaceuticals, Plot No. 442, Street No. 7, I-9/2, Industrial Area, Islamabad.
12.	Harmann Pharmaceutical Labs (Pvt) Ltd,, 16 -Km Multan Road, Lahore.,
13.	M/s Hicon Pharmaceuticals. 131-Industrial Estate, Hayatabad , Peshawar.
14.	M/s. Hisun Pharmaceutical Industry, 37-A R-02 Industrial Estate Gadoon Amazai, District Swabi.
15.	Irza Pharma (Pvt) Ltd, 10/2 Km Sheikhupura Road, P.O. Kot Abdul Malik, Sheikhupura.
16.	M/s. Kohs Pharmaceuticals (Pvt) Ltd., Plot No. P/8 S.I.T.E, Hyderabad.
17.	Life Pharmaceutical Company, 24-III, Industrial Estate, Multan
18.	Mediceena Pharma (Pvt) Ltd, , 27-K.M, Raiwind Road, Lahore
19.	M/s. Medicraft Pharmaceuticals (Pvt.) Ltd.,126-B Industrial Estate Hayatabad, Peshawar.
20.	Metro Pharmaceuticals, Plot No. 14 St. No. SS-2 National Industrial Zone (RCCI) Rawat Islamabad.
21.	Neomedix , Plot No.5, N-5 National Industrial Zone Rawat (Islamabad).
22.	Olive Laboratories Plot No.52-S-6 National Industrial Zone Rawat Rawalpindi.
23.	M/s. Onyx Pharmaceuticals Industries, 30-A Industrial Estate Mansehra.
24.	Previous Address: Mac & Rains Pharmaceuticals (Pvt) Ltd, 1.5 KM, Manga Raiwind Road, Manga Mandi, Lahore. Current Address: M/s Searle IV Solutions (Pvt) Ltd, 1.5 KM, Manga Raiwind Road, Manga Mandi, Lahore.
25.	Rasco Pharma, 5.5 KM Raiwind Road Ali Razabad, Lahore,
26.	M/s. Regent Laboratories C-20, S.I.T.E Super Highway, Karachi

27.	Selomore Pharmaceuticals (Pvt) Ltd.,35 KM, Multan Raod, lahore
28.	M/s T.G. Pharma, E-30 Sector 15, Korangi Industrial Area, Karachi. [Previous Title: M/s. Unicorn Pharma] Karachi
29.	Theramed Pharmaceutical, 331-J-1 Johar Town Lahore,
30.	Wilshire Laboratories, 124/A, Kotlakhpat, Indus. Area, Township Scheme, Lahore.,
31.	M/s. Synchro Pharmaceuticals 77-Industrial Estate Kot Lakhpat Lahore.

Annexure-B

Attendees Having Agreement with RB Decision			
Sr. No.	**Registration Holder**	**Statement of Agreement**	**Name & Designation of Representative (Attendees)**
1.	Akson Pharmaceuticals Co. (Pvt.) Ltd.	The firm agreed with the decision of Registration Board for all registration holders.	Mr. M. Azeem Q.C.M
2.	M/s Atco Laboratories Ltd, B-18, S.I.T.E, Karachi.	The firm agreed with the decision of Registration Board for all registration holders. Further they have submitted that in USFDA 10mg Tablet is also registered but they have not provided any data confirming that both 10mg Tablet and Suspension have same efficacy profile or any document regarding efficacy of 10mg suspension.	Mr. Amjad Butt & Mr. Azhar Zaidi
3.	M/s Bloom Pharmaceuticals Pvt. Ltd, Plot # 30, Phase I & II, Industrial Estate, Hattar.	The firm agreed with the decision of Registration Board for all registration holders.	Mr. Farhan Liaqat Manager Regulatory Affairs
4.	M/s. Brookes Pharma (Pvt) Ltd., Plot No. 58-59, Sector No. 15, Korangi Industrial Area, Karachi.	i. They have stated that 10mg/5ml is used as an Antacid by Doctors and 40mg/5ml is used as anti-Ulcer. ii. The firm agreed with the decision of Registration Board for all registration holders.	Mr. Arshad M.Awan
5.	Global Pharmaceuticals, Plot No 204-205, Kahuta Triangle, Industrial Area, Islamabad	i. The firm agreed with the decision of Registration Board for all registration holders. ii. They also wanted to convert to 40mg/5ml dry suspension.	Mr. M. Suleman Regulatory Manager
6.	Gulf Pharmaceuticals, Plot No.4, St.No. S-6, National Industrial Zone, Rawat,	The firm agreed with the decision of Registration Board for all registration holders. However, firm has requested to give time to utilize the existing stock of finished products.	Mr. Shuja-ul- Hassan M. Khalique
7.	M/s. Helix Pharma Pvt. Ltd., A-56, Manghopir Road S.I.T.E., Karachi.	The firm agreed with the decision of Registration Board for all registration holders.	Syed Shehzad Regulatory Manager
8.	Max Pharmaceuticals, Rawalpindi	The firm agreed with the decision of Registration Board for all registration holders.	Waqar Muhammad Project Manager
9.	M/s. Meditech Pharmaceuticals, 15-D Industrial Estate, Jamrud Road, Peshawar,	The firm agreed with the decision of Registration Board for all registration holders.	Faisal
10.	M/s. Polyfine Chempharma, 51 Industrial Estate, Hayatabad, Peshawar.	The firm agreed with the decision of Registration Board for all registration holders.	Faisal
11.	Previous Address: Mac & Rains Pharmaceuticals (Pvt) Ltd, 1.5 KM, Manga Raiwind Road, Manga Mandi,	The firm agreed with the decision of Registration Board for all registration holders.	Yasir Yaqoob DM Regulatory

	Lahore. Current Address: M/s Searle IV Solutions (Pvt) Ltd, 1.5 KM, Manga Raiwind Road, Manga Mandi, Lahore.		
12.	Trigon Pharmaceutical (Pvt) Limited, 18 Km Raiwind Road, Lahore	The firm agreed with the decision of Registration Board for all registration holders.	Asad Khan Regulatory Manager
13.	Xenon Pharma, Lahore.	The firm agreed with the decision of Registration Board for all registration holders.	Adeel Shaikh Assistant Regulatory Manager
14.	M/s. Zafa Pharmaceutical Laboratories (Pvt.) Ltd., L-1/B Block 22 Federal B Industrial Area, Karachi	The firm agreed with the decision of Registration Board for all registration holders.	Irfan Habib QRM
15.	Werrick Pharmaceuticals, 216-217, I-10/3, Industrial Area, Islamabad.,	The firm informed that they are switching over to standard formulation i.e. Famotidine 40mg/5ml Dry suspension.	M. Tauqeer QCM

Annexure-C

Attendees Having Disagreement/ Varying Stance			
Sr. No.	**Registration Holder**	**Statement/ Stance**	**Name & Designation of Representative (Attendees)**
1.	Ambrosia Pharmaceuticals, Plot No.18, St. No.9, National Industrial Zone, Rawat, Islamabad.,	i. Available in China which covers 3.6 billion of total population and also available in India. ii. Firm was asked to provide data on which basis approvals were granted in India then firm replied that they have no data. iii. No ADRs are reported till now. iv. Firm has asked the Board that on which basis Board has issued notice to the firm. Board replied that the bases are Section 7 (11) (d) of the Drugs Act, 1976.	Mr. Jaafar
2.	Hamaz Pharmaceuticals (Pvt) Ltd,, 22 Km Lutafabad Road, Multan.,	i. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic ii. They have submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11) . iii. Their product is registered and being marketed since many years and no ADRs are reported till to date which establishes that product is safe and effective. iv. Hence, the said product may not be cancelled and show-cause may be revoked.	Mr. Atif Shah Regulatory Manager
3.	Jawa Pharmaceuticals (Pvt.) Ltd.,	iv. It's an old registration. v. Doctors are satisfied vi. No market complaint has been reported till to date. vii. In response to question asked it was replied that no efficacy data is not available with the firm.	Muhammad Ali Assistant Manager QC
4.	Lawrence Pharma (Pvt.) Ltd, 10.5Km Sheikhupura Road, Lahore.,	Firm informed that Technical person is not available and they will submit written response which is not received till now.	Kashif Adnan
5.	M/s Lowitt Pharma (Pvt) Ltd.,Plot No.24-Industrial Estate, Hayatabad, Peshawar.	i. Registered for 10 to 11 years. ii. Preferred by Doctors. iii. No market complaint has been reported till to date. iv. In response to question asked it was replied that no efficacy data is not available with the firm. v. Dose calculation and administration in easy in 10mg/5ml.	Syed Zahir Ali Plant Manager
6.	M/s Macter International Limited. F-216, S.I.T.E, Karachi.	i. Representative of M/s. Cibex Mr. Malik Zamir appeared and he was asked to submit registration letter of product registered in the name of M/s. Cibex.	Representative of M/s. Cibex Mr. Malik Zamir appeared on behalf of M/s. Macter. Representative of M/s. Cibex was advised to

		ii. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic iii. They have submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). iv. Their product is registered and being marketed since many years and no ADRs are reported till to date which establishes that product is safe and effective. v. Hence, the said product may not be cancelled and show-cause may be revoked.	submit authority letter otherwise your presence cannot be considered but he has not submitted authority letter.
7.	Medisearch Pharmacal, Lahore.	i. Their product is registered since 2004 and no ADRs are reported till now as product is safe and effective. ii. Firm was asked question to submit data regarding efficacy of said product and firm replied that they have no data. iii. This product is largely used in India and China.	Farhan Khalid
8.	Medley Pharmaceutical, 41-A P.S.I.E Jhang Bahtar Road, Wah Cantt,	Registered since, August, 2009 and no ADRs are reported till now as product is safe and effective. Firm has no clinical data regarding its efficacy.	Asad Mughal Production Manager
9.	Miracle Pharmaceuticals (Pvt.) Ltd., Islamabad,	With the cancellation of 10mg/5ml product's market will be affected. The firm has relevant section & may revise their formulation as per RRA.	Muhamamd Naveed QCM Aftab Safdar Procurement
10.	Neutro Pharma (Pvt) Ltd, 9.5Km,SheikhupuraLahore,	i. In China, India Famotidine 10mg is available which covers 38% of world population. It is also available in USA. ii. No ADRs were also reported in these countries nor any clinical trial data is available in these countries. iii. Their product is registered and being marketed since many years and no ADRs are reported till to date which establishes that product is safe and effective. iv. In BNF recommended daily dose is 10mg. v. In Drugs.com, recommended dose in Hyper-acidity is 10mg followed by 20mg and In Dyspepsia, Heart Burn, recommended dose is in divided doses of 10mg twice daily. vi. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic.	Nazia

		vii. Hence, the said product may not be cancelled and show-cause may be revoked. viii. Further they have requested to consider application for conversion on For-5 instead of CTD.	
11.	M/s Platinum Pharmaceuticals (Pvt) limited, A-20 North Western Industrial Zone, Bin Qasim, Karachi	Although no efficacy data is available with the firm. However, MRP of Famotidine 40mg/5ml Dry Suspension is not viable.	Fahim Lakhani Plant Manager
12.	Previous Address: Evergreen Pharmaceuticals (Pvt) Ltd, Plot No. 590, Sundar Industrial Estate, Lahore. Current Address: M/s Allmed (Pvt) Ltd, Plot No. 590 Sundar Industrial Estate, Lahore	i. Registered since 14 years. ii. No efficacy data is available. iii. Reference was made to 70th meeting of Authority.	Feroz Ahmad Manager Regulatory Affairs
13.	Scotmann Pharmaceuticals, 5D, I-10/3 Industrial Area, Islamabad	i. They have already applied fresh application for registration of 40mg/5ml dry suspension. ii. Dose of 10mg is also safe in patients having compromised renal clearance. iii. 10mg is also available in dispersible tablet dosage form in USFDA. iv. Dose adjustment is easy in 10mg/5ml as compared to 40mg/5ml.	Muhammad Amir DGM Tipu Sultan Akram GM Muhamamd Bilal DMRA
14.	Shaigan Pharmaceutical (Pvt) Ltd., 14-Km Adyala Road Post Office Dahgal Rawalpindi, Pakistan	Registered since 2000. No ADRs are reported.	Dr. Musarat Zulfiqar
15.	Raazee Therapeutics (Pvt) Ltd., 48-Km Lahore Kasur Road Kasur., Kasur, , Pakistan	i. Their product is in market for 20years and no ADRs are reported till now for this product nor for any other product as ADRs reporting system is available with the firm. ii. In BNF recommended dose is 10mg. iii. In USFDA 10mg Tablet is also registered. iv. In case of Hyper-acidity recommended dose 10mg followed by 20mg. v. In Dyspepsia, Heart Burn, recommended dose is in divided doses of 10mg twice daily. vi. A question was raised that do you have any data confirming that both 10mg Tablet and Suspension have same efficacy profile or any document regarding efficacy of 10mg suspension. Then firm has replied that no data is available	M. Saddiq Malik GM Regulatory Affairs

		and time may be given for clinical trials. vii. They will also apply for registration of dry suspension dosage form.	
Firms Responded through Written Arguments			
Sr. No.	**Registration Holder**	**Written Argument/ Statement**	
16.	M/s Barrett Hodgson Pakistan (Pvt) Ltd. F/423, S.I.T.E., Karachi.	Our technical person who will participate in case and know all the relevant facts is on leave. Therefore, we urge and request you to kindly defer and grant us an adjournment to a next date of hearing wherein we shall make sure to participate with full facts and evidence of the case under discussion.	
17.	M/s. Prime Labs (Pvt) Ltd, 9.5 Km Sheikhupura Road, Lahore.,	Their product is available in market since last 17 years and no ADRs have been reported till now. They have quoted the reference of 70th meeting of Authority	
18.	M/s Adamjee Pharmaceuticals (Pvt.) Ltd., Plot 39, Sector 15, Korangi Industrial Area, Karachi.	Please cancel the said products after complete utilization of the packaging materials of the said products.	
19.	Helicon Pharmaceutek, Pakistan (Pvt) Ltd,, Model Town Road, Faisalabad,	i. This drug was registered on 09.08.2003. Thus, has a prescriber doctor's confidence in the brand. It is very long procedure for new registration. ii. Whereas we also have been granted Cantil 40mg tablet (Famotidine) under registration no. 016854. The patients who could not take tablet and have to choose take suspension according to the doctor's prescription. iii. Therefore, in the interest of patients and prescribing doctors we request for substituting the formulation from 10mg/5ml to 40mg/5ml in suspension form. iv. Necessary approvals may kindly be granted for complying with the decision of Registration Board in peculiar circumstances of our case of change of strength of our registered formulation namely Cantil Suspension registration no. 030273 from 10mg/5ml to 40mg/5ml. We follow the SOP's in this regard.	
20.	M/s Macquin's International, F-2/H, PTC Industrial Complex S.I.T.E, Karachi.	i. It is respectfully submitted that our CEO is suffering from Covid 19 he will be available as per doctor Prescription in mid-February, ii. It is therefore humble requested he may please be allowed to appear before the Registration Board for Personal hearing by 10 February 2022. We shall remain grateful in anticipation for granted us one month time on medical ground.	
21.	M/s Sayyed Pharmaceutical (Pvt) Ltd.,Plot No. 67/2, Phase 3, Industrial Estate, Hattar. Haripur	i. In Martindale 38th edition volume 2, Page 1842 famotidine is licensed for use in children in some countries, including the USA, It is used to inhibit gastric acid secretion and may be given orally in the management of gastro esophageal reflux disease, the following initial oral doses of famotidine are suggested, according to age, Under 3 months: 500 micrograms/kg once daily. 3 months up to year: 500 microgram/kg twice daily. 1-16 Years: 500 micrograms/kg twice daily up to 40mg twice daily may also be given. i. In the management of peptic ulcers, famotidine may be given to children from 1 to 16 years in an initial oral dose of 500 micrograms/kg daily either in a single dose at night or in 2 divided doses ii. However, we will apply to change our drug product from S-famers 10mg Syrup (Famotidine 10mg/5ml) Reg No. 064293 to famotidine 40mg 5ml dry powder for Suspension as per decision of the honorable registration board.	

22.	M/s. Z-Jans Pharmaceuticals (Pvt) Ltd., 148-A, Industrial Estate Hayatabad, Peshawar.	i. It is stated that we will be agree with collective decision of the honorable board regarding our afore said product if the decision was for all the manufacturer in Pakistan. ii. You are hereby requested that grant us registration of the same product in Dry Suspension 40mg/5ml in mutual.
23.	Unison Chemical Works, 15 Km Raiwind Road Lahore., Lahore	v. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic vi. They have submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). vii. Their product is registered and being marketed since many years and no ADRs are reported till to date which establishes that product is safe and effective. viii. Hence, the said product may not be cancelled and show-cause may be revoked.
24.	Fynk Pharmaceuticals, 19 K.M. G.T. Road, Kala Shah Kaku, Lahore	i. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic ii. They have submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). iii. Their product is registered and being marketed since many years and no ADRs are reported till to date which establishes that product is safe and effective. iv. Hence, the said product may not be cancelled and show-cause may be revoked.
25.	Epharm Laboratories, A-40, Road No. 1, S.I.T.E. Super Highway Industrial Area, North Zone, Karachi	i. Non-availability of said products in RRAs does not establish that the product is unsafe or toxic ii. They have submitted that personal hearing letter has no legal value as there is no violation of provision of Section 7(11). iii. Their product is registered and being marketed since many years and no ADRs are reported till to date which establishes that product is safe and effective. iv. Hence, the said product may not be cancelled and show-cause may be revoked.

Annexure D

Attendees who have filled Court cases			
Sr. No.	**Registration Holder**	**Statement/ Stance**	**Name & Designation of Representative (Attendees)**
1.	Paramount Pharma, 36, Industrial Triangle Kahuta Road, Islamabad,	ii. It's an old registration. iii. Doctors are satisfied iv. No market complaint has been reported till to date. v. In response to question asked it was replied that no efficacy data is not available with the firm.	Tasleem Ul Haq Manager Regulatory Affairs
2.	Siza International (Pvt) Ltd, 18 KM, Main Ferozepur Road, Lahore	i. Their product is in market for 20years and no ADRs are reported till now for this product nor for any other product as ADRs reporting system is available with the firm. ii. In BNF recommended dose is 10mg. iii. In USFDA 10mg Tablet is also registered. iv. In case of Hyper-acidity recommended dose 10mg followed by 20mg. v. In Dyspepsia, Heart Burn, recommended dose is in divided doses of 10mg twice daily. vi. A question was raised that do you have any data confirming that both 10mg Tablet and Suspension have same efficacy profile or any document regarding efficacy of 10mg suspension. Then firm has replied that no data is available and time may be given for clinical trials. vii. They will also apply for registration of dry suspension dosage form.	M. Saddiq Malik GM Regulatory Affairs
Non-Attendees who have filled Court cases			
Sr. No.	**Registration Holder**		
4.	M/s Pakistan Pharmaceutical Products (Pvt) Ltd., D-122, Sindh Industrial Trading Estate, Karachi.		
5.	Shrooq Pharmaceutical (Pvt) Ltd, 21-KM, Feroze Pur Road, Lahore		
6.	M/s. Cibex (Pvt) Ltd. F-405 S.I.T.E Karachi 000784		

Case No.3. Personal Hearing Notices issued to the Registration Holders of Irrational combination - Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg.

Registration Board in its various meetings considered the subject mentioned case and finally in its 313th meeting held on 16th-18th Nov, 2021 decided to provide the opportunity of personal hearing to the following registration holders:

S.No.	Reg. No.	Product Name & Composition	Registration Holders
1.	015654	Diagesic-P Tablet Each tablet contains: Paracetamol……500mg Thioridazine……..3mg Caffeine……70mg	M/s Wilson's Pharmaceuticals, 387-388 Sector I-9 Industrial Area Islamabad.
2.	063092	Pregesic Tablet Each tablet contains: Paracetamol……500mg Thioridazine……..3mg	Existing Title: M/s ICI Pakistan Ltd., [Previous Title: M/s Cirin Pharmaceuticals (Pvt.) Ltd.]

		Caffeine……70mg	32/2A, Phase III, Industrial Estate, Hattar.

Complete record of the case including previous proceedings and decisions of Registration Board have been reproduced as under:

1. Proceedings of M-263 held on 29th -30th Nov, 2016:

A combination of Paracetamol 500mg, Thioridazine 3mg and Caffeine is registered in Pakistan by the name of tablet Diagesic P of Wilson's Pharmaceutical Islamabad Registration no. 015654 and tablet Pregesic of Cirin Pharmaceutical Hattar Registration no.063092. The said combination is routinely prescribed by the physicians as analgesic and also is sold as OTC medicine by the pharmacies and medical store.

Thioridazine, a conventional anti-psychotic drug which was used in Schizophrenia and was discontinued in most of the western countries. Novartis had issued dear health care professional letter in July, 2000 for its research product Mallaril (thioridazine) regarding black box warning of QTc interval prolongation, arrhythmia (abnormal heart rhythm that can lead to sudden cardiac arrest), sudden death and limit its use only for schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other anti-psychotic drugs. In 2005 Novartis announced to discontinue all form of Thioridazine worldwide due to its questionable benefit risk profile. Moreover, the said combination is not registered in any stringent regulatory authorities (Canada, EU, FDA, PMDA, TGA and MHRA).

Rule 30(10)[a] of Drug (Licensing, Registering & Advertising), 1976 in respect of registered drugs shall be complied with the following provisions of the rule, stated as under:

"30(10). If a drug or any of its ingredients, which is imported or manufactured by a company in Pakistan is also approved for registration and free sale by its subsidiary, sister concern, associate or parent company in the country where it was originally developed or in any of the countries namely, U.S.A, European Union Countries, Canada, Japan, Australia and—

a. if that drug at any time, for safety reasons is withdrawn or banned or certain restrictions are imposed in any of the said countries, then it shall be the responsibility of the manufacturer in Pakistan or the case may be, the inventors, to immediately withdraw the drug from the market in Pakistan or, as the case may be to impose similar restriction and to inform the Registration Board within fourteen days of such an information having come to his knowledge and having taken the necessary action. The Registration Board after getting the said intimation shall take similar action for the same drugs available from other sources with the shortest possible time;"

The case was placed in 263rd meeting of Registration Board and Board decided as under;

2. Decision of M-263 held on 29th -30th Nov, 2016:

i. The combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) is not available in any of the reference regulatory authorities as approved by the Board i.e. FDA, TGA, EMA, PMDA, MHRA, Health Canada, Germany, France, Switzerland, Sweden, Norway, Denmark, Austria and Netherland. Since, it is reported vide WHO newsletter no.1, 2005 about voluntary withdrawn of Thioridazine worldwide by the brand leader Novartis, hence all irrational combinations containing Thioridazine, which are also not existent worldwide be also withdrawn throughout the country.

ii. Show cause notice will be served by the concerned Registration section to Wilson's Pharmaceutical Islamabad and Cirin Pharmaceutical Hattar for de-registration of drug.

iii. Advised PE & R Division to confirm/status of registration of the said combination (other than two brands i.e. Diagesic-P and Pregesic) and inform Registration Board to initiate process for de-registration of products.

3. Proceedings of M-293 held on 06th-08th Jan, 2020:

The Board was informed that show cause notices were served to M/s. Wilson Pharmaceutical, Islamabad and M/s. Cirin pharmaceutical, Hattar regarding cancellation of registration under Drugs Act 1976 and rules framed there under. Later on, M/s. Wilson Pharmaceutical, Islamabad filed a case in the Court of Senior Civil Judge (West) Islamabad. The Court vide their order dated 01-11-2018 rejected plaint under order VII rule 11 of CPC.

It is pertinent to mention here that Provincial Drug Inspector, Nowshera has informed that the Registration Board in its 263rd meeting decided regarding the registration of Tablet Diagesic-P of M/s. Wilson Pharmaceuticals, Islamabad on account of safety and efficacy concerns. He has seized the said drug product from multiple sales outlets at district Nowshera and then served show cause notice to M/s. Wilson, Islamabad. In response, Mr. Tepu Sultan Akram, General Manager of M/s. Wilson Pharmaceuticals Islamabad replied him that registration of Diagesic-P Tablet (Reg.No.015654) is still intact and renewed regularly from the DRAP and no proceeding regarding the cancellation/de-registration of Diagesic-P Tablet is initiated by DRAP. He has therefore, requested for final decision by DRAP in the case to further proceed in the matter.

4. ***Decision of M-293 held on 06th-08th Jan, 2020*:**

   Registration Board deliberated on the matter in details and decided to give an opportunity of personal hearing as per Drug Act, 1976 and Rules framed there under to both the firms i.e M/s. Wilson Pharmaceuticals, Islamabad & M/s. Cirin Pharmaceuticals, Hattar in forthcoming meeting of Registration Board.

5. **Reference received from Shifa International Hospital dated 18th Oct, 2021:**

   'Thioridazine' originally marketed by the brand name of Melliril by Novartis, was voluntarily recalled due to serious cardiac side effects and later many other countries suspended its usage/ registration or imposed restrictions for use. However, in Pakistan this medicine is still available by the name 'Diagesic-P' tablets (manufactured by Wilson Pharmaceuticals). Pharmacovigilance system in Pakistan is in rudimentary stage and how many patients have suffered/ are suffering due to this medicine is unknown. So in the best interes of patient safety it is requested that company is to be directed by DAP to remove this medicine Thioridazine from its combination product Diagesic-P.

6. ***Decision of M-313 held on 16th-18th Nov, 2021*:**

   Registration Board discussed that as show-cause notices have already been issued to M/s Wilson Pharmaceuticals, Islamabad and M/s Cirin Pharmaceuticals (New Title: ICI Pakistan Ltd.), Hattar, therefore, Registration Board decided that management of above-mentioned firms shall be given the opportunity of personal hearing in the forthcoming meeting of the Board under section 42 of the Drugs Act, 1976.

Accordingly, notices have been issued to registration holders of "Diagesic-P" & "Pregesic" Tablet for personal hearing before the Registration Board on 17th May, 2022 at 10:00 A.M.

Proceedings During 317th Meeting:

1. The instant proceedings have been undertaken in pursuance of decision taken by the Registration Board in its 263rd wherein Show Cause were issued to all registration holders of fixed dose combination containing Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg under Section 7(11) (b, c & d) and Rule 30(10)(a) of Drugs (Licensing, Registering & Advertising) Rules, 1976 for cancellation or suspension of registration of the aforementioned in the public interest. The Show Caused registration holders of the drug in question were also issued personal hearing notices under Section 42 of the Drugs Act, 1976 and were heard at length.

2. Despite of show cause notice issued to the two companies which hold registration of above- mentioned formulation, M/s Cirin Pharmaceuticals (Pvt.) Ltd. (Existing Title: ICI Pakistan), 32/2A, Phase III, Industrial Estate, Hattar did not avail the opportunity of personal hearing while, M/s Wilson's Pharmaceuticals, 387-388 Sector I-9 Industrial Area Islamabad appeared before Registration Board and presented their case.

3. The arguments raised in brief in reply to the notice as well as during personal hearing were that the registration reference for their product "Diagesic-P Tablets" was "Optagesic Tablets (containing the same ingredients)" which was marketed by Sandoz Pakistan in 1994 and widely prescribed by doctors and freely available in the global market. Later on, Novartis came into being after the merger of Sandoz and Ciba Geigy in 1996. The marketing portfolio of the newly established Novartis did not contain Optagesic. The marketing of Optagesic was therefore discontinued due to commercial reasons. The Board in its 263rd Meeting without conducting any proper fact finding enquiry decided to issue show cause notices by disregarding that the drug had subsisted over a period of last 26 years without any reported adverse effects. While referring to the minutes of 296th meeting, the firm has stated that system for recording evidence of ADRs and their evaluation is not well established till to date, therefore, the absence of such data in itself is a stopple for any proceeding whatsoever for de-registration of Diagesic-P Tablet. Furthermore, the firm has contended that until now since the first show cause served in 2017, the drug has not been evaluated considering scientific grounds, therapeutic equivalencies and pharmacodynamic aspects as deliberated by the Board vide the same 296th meeting with respect to those products which have been withdrawn by the Reference Regulatory Authorities due to marketing/ commercial reasons. Therefore, the present exercise of issuance of show cause notice is uncalled for & premature. Moreover, grounds of show-cause are also baseless as 3mg Thioridazine in Diagesic-P Tablet is being compared with Mellaril (Thioridazine) which is available in strengths of 10mg to 200mg.
4. Record has been perused with the able assistance of the representatives of the registration holder and arguments have been heard.
5. As per USFDA, Thioridazine Hydrochloride tablets (10mg-200mg) are indicated for the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Due to the risk of significant, potentially life threatening, proarrhythmic effects with thioridazine treatment, thioridazine hydrochloride tablets should be used only in patients who have failed to respond adequately to treatment with appropriate courses of other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. The usual starting dose for adult schizophrenic patients is 50 mg to 100 mg three times a day, with a gradual increment to a maximum of 800 mg daily if necessary. Considering one of the arguments that Diagesic-P (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) contains only 3mg of thioridazine which may not be associated with the aforementioned ADRs, it is to be noted that data supporting safety and efficacy of 3mg thioridazine in a formulation which also contains 'Caffeine' and 'Paracetamol' is not available in any RRA nor any safety and efficacy data submitted by the pharmaceutical firms.

6. Succinctly stated the facts of the matter are that the Registration Board in its various meetings considered the case of, *inter alia*, fixed dose combination containing Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg i.e. the drug product in question. Although, the concern initially raised when it was reported vide WHO newsletter no.1, 2005 about voluntary withdrawn of Thioridazine worldwide by the brand leader Novartis. Later on, it was concluded that from the available record and reviewing of information available from the Reference Regulatory Authorities ('**RRAs**') that although generic versions of Thioridazine Tablets (10mg-200mg) are approved and still available in RRAs in comparison to which the fixed dose combination of Diagesic-P (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) contains far less quantity/strength of thioridazine. However, data regarding safety and efficacy of the instant combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) is neither available in RRAs nor any data to establish safety and efficacy has been submitted by any pharmaceutical concern. Hence, continuing registration of the formulations was not considered justifiable keeping in view safety and efficacy parameters which are mandatorily required for continuing with registration of any drug. Therefore, it was decided in the 263rd Meeting dated 29th and 30th February, 2016 to issue Show Cause Notices to the registration holders in accordance with the law explained above, to seek response as to why the registrations should not be cancelled.

7. In the meanwhile, DRAP Authority in its 70th Meeting held on 05-09-2019 decided the following:

> *"For formulations containing "drugs" which were previously registered by the Registration Board and have proof of availability and prescription of last 10 years but are not available in the Reference Regulatory Authorities shall continue to be considered/ registered as drugs until and unless withdrawn on Safety, Efficacy and Quality reasons."*

8. Subsequently, Registration Board in its 296th Meeting held on the 8th-10th September, 2020, decided to request the DRAP Authority to review its above mentioned decision in the following words:

> *"Since, all such formulations which are not approved by the Reference Regulatory Authorities; the safety and efficacy profile cannot be established in the absence of a well-established system for reporting of adverse events, so a reference shall be forwarded to DRAP's Authority with the request to review the decision taken in its 70th meeting held on 05-09-2019. In this regard, PE&R Division shall prepare a comprehensive document/agenda for consideration of Authority, keeping in view the practices adopted by RRA for all such formulations;"*

9. The DRAP Authority in its 128th Meeting held on 14-12-2021 was pleased to accept the request the Registration Board and reviewed its 70th Minutes in the following words:

The Authority endorsed the recommendation of Registration Board and made following decisions:-

A. Partially reviewed its earlier decision taken in its 70th meeting held on 05-09-019, consolidated amended decision is reproduced as under:

[…]

4. Drug formulations/ strengths which are previously registered by the Registration Board but are not available in any Reference Regulatory Authorities, shall be reviewed and disposed of keeping in view of safety and efficacy evidence/ data in the reference Regulatory Authorities."

10. In pursuance of the above mentioned, Registration Board in 313th Meeting decided to issue Personal Hearing Notice to all registration holders of fixed dose combination containing Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg under Section 42 of the Drugs Act, 1976 for cancellation or suspension of registration of the aforementioned in the public interest. Therefore, in pursuance of the decision by the DRAP Authority taken in its 128th Meeting, the instant proceedings are being undertaken.

11. It is to be noted at the outset that registration or licensing has been held by the Superior Courts to be a privilege not a right which can always be cancelled or suspended in accordance with the law. It has argued at length that the Registration Board granted registration after determining safety and efficacy of drugs which was renewed over time, therefore, the Board cannot after passing of many years re-assess the safety and efficacy of drugs. The argument is fallacious as Rule 27 of the Drugs (Licensing, Registration and Licensing) Rules, 1976 ('**Rules, 1976**') while providing the duration of drug registration also added that the registration can always be cancelled or suspended earlier as well. The grounds on which the drug registration can be suspended or cancelled are provided in Section 7 (11) of the Drugs Act, 1976, and therefore, the argument that registration once granted will continue forever on the basis of its market life is against the law. Furthermore, Section 21 of the General Clauses Act, 1897, grants the Board the power to rescind any drug registration so made in accordance with the grounds provided in Section 7 (11) of the Drugs Act, 1976. The argument in discussion is also fallacious for the reason that scientific pharmaceutical knowledge is always in the process of evolution and decision based on knowledge available at one point of time cannot be used to defeat the just and fair decision to be taken in future with the broadening of knowledge. This principle has been encapsulated in Rule 30 (12) of the Rules, 1976, which grants the Board power to seek any information at any point in time post-registration regarding the safety and efficacy of drugs. The Board has ample powers under Rule 30 (2) to rescind, vary or modify any decision taken by it in the larger public interest to perform its statutory regulatory duty of ensuring the provision of safe and efficacious drugs and medicines to the public at large.

12. Applicant companies are generic drug product manufacturers. The generic drug product is pharmaceutically equivalent to the innovator's drug product as it contains the identical medicinal ingredients in the same amount/strength and dosage form and it must have same pharmacokinetics, pharmacodynamics, indications, contraindications, side effects etc. A generic drug product must work in the same way as that of innovator's drug product and, therefore, it can be interchanged with the innovator's drug product. As status of innovator's drug product 'Optagesic Tablet (as claimed by M/s Wilson, Islamabad)' is not accessible and M/s Wilson, Islamabad has not submitted any data supporting safety, efficacy and the then approval status in RRAs of "Optagesic Tablet". Furthermore, applicant companies have neither conducted nor provided any safety and efficacy study to establish the aforementioned points (i.e., pharmacokinetics, pharmacodynamics, indications, contraindications, side effects etc.).
13. The primary ground which has prevailed with the Board for initiating the instant proceedings is that the drug in question is neither approved by any of RRAs nor any data regarding safety and efficacy of fixed dose combination containing Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg is available. Furthermore, in this regard, the firm's stance stating withdrawal of aforementioned combination is due to commercial reasons could neither be verified from any source nor M/s Wilson was able to provide any document to substantiate their claim. To better appreciate the argument, it is important to understand the scheme of the law which allows for placing reliance on RRAs as well as its importance for performing the statutory regulatory duties.
14. Criteria for grant of registration of any drug product is safety, efficacy and quality parameters and the onus for provision of relevant data onus for provision of relevant data to establish aforementioned parameters under the applicable law is upon the applicant/registration holder. For this purpose, applicant either needs to provide sufficient data to satisfy the aforementioned parameters by themselves, or provide reference to approval of registration granted by any Reference Regulatory Authorities ('**RRAs**'); this serves the purpose for determining safety and efficacy of the drugs. Reference Regulatory Authorities ('**RRAs**') are regulatory authorities of developed countries which have stringent regulatory regimen. They have developed robust mechanisms for determining drug safety, efficacy and quality and their decisions are supported by the rapid advances in sciences as well as empirical studies. Even WHO supports the reliance by developing countries on decisions of the Stringent Regulatory Authorities, to avoid redundancy, global harmonization of standards and wastage of limited regulatory and financial resources. This reliance enables Registration Board to have evidence for robust and accurate decision-making, considering that the products registered and sold in the countries of reference regulatory authorities have already been strenuously evaluated to fulfil the harmonized standards of safety, efficacy and quality as adopted by WHO, ICH, etc. This reliance also

enables DRAP being the national regulatory authority in undertaking post marketing surveillance, particularly of matters related to safety and efficacy of drug. RRAs have stronger reporting and information sharing system, which can be used by DRAP as a national regulatory authority as a useful tool for surveillance, new available treatments and new indications or contra-indications.

15. It is pertinent to mention that since adoption of RRA, DRAP has approved only those drug products which are either approved by RRAs based on their safety and efficacy assessment or after provision by the applicant pharmaceutical concern of relevant data regarding their safety, efficacy and quality. Moreover, DRAP has also started review process of already registered drugs to ensure availability of quality assured safe and effective therapeutic goods to ailing patients in the larger public interest.
16. The Registration Board in accordance with the global best practices, in its 275th Meeting held on 25th to 27th of October, 2017, decided to adopt the RRAs and their decisions "as reference for molecules/ formulations as reference for molecules/ formulations (in same dosage form and strengths) along with clinical trials for human purpose." The aforementioned decision has since been applied by the Registration Board and also been followed by all pharmaceutical concerns without any caveat. Currently, all registered formulations and dosage of drugs and medicines in Pakistan are now required to comply with the details/ specifications as approved by RRAs or provide sufficient data for assessing safety, efficacy and quality of the drug product. Aforementioned decision has been taken to ensure availability of quality assured safe and effective medicines to ailing patients as it is matter of prime public health concern.

17. The adoption of RRAs allows the performance of the statutory duty to "adopt […] standards and guidelines to ensure safety, efficacy, and quality of therapeutic goods" as ordained under Section 7 (t) of the DRAP Act, 2012. Therefore, the DRAP Authority *[created under Section 2 (iv) and Section 7 of the DRAP Act, 2012]* also approved the policy of reliance on RRAs in its 73rd Meeting held on 06-11-2019. Hence, the argument that reliance on RRAs is without any basis for determining safety and efficacy of the drug which is not available in RRAs and, therefore, data regarding its ADRs is lacking. Furthermore, as all pharmaceutical concerns are effectively complying with decision by the Board regarding reliance on RRAs in approval of their drug products and have never raised any objection or caveat to it, therefore, they are restrained and estopped by their own conduct from challenging the reliance on RRAs.

18. As the legality of reliance on RRAs has been detailed above, the Board has initiated instant proceedings after conducting thorough inquiry of the registration and availability of the fixed dose combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) in

RRAs. Although, WHO newsletter No.1, 2005 (about voluntary withdrawn of Thioridazine worldwide by the brand leader Novartis) was one of the prime reasons for initiating proceedings of show cause notice issued in 2017. However, responding to one of the arguments raised by M/s Wilson i.e., 3mg of Thioridazine in 'Diagesic-P Tablet' is being irrationally compared with higher strengths (10mg-200mg) of Thioridazine in 'Mellaril' which was commercially withdrawn, it is acknowledged that although generic versions of Thioridazine Tablets (10mg-200mg) are approved and still available in RRAs. Furthermore, the fixed dose combination of Diagesic-P (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) contains far less quantity/strength of thioridazine. However, it is reiterated that the instant combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) has neither been approved by RRAs nor any pharmaceutical concern has submitted data supporting its safety and efficacy, both of which are ultimate grounds for initiating instant proceedings.

19. In taking high risk decisions such as determining the safety and efficacy of drugs, the globally accepted principle is to err on the side of caution and adopt the most stringent standards in the largest public interest. The Superior Courts in Pakistan have in various pronouncements held matters related to safety and efficacy of drugs to be directly affecting the constitutionally protected right to life of the people for which highest care and caution is to be adopted by the regulatory authority. It has also been held by the Hon'ble Court that in matters which affect the life and health of the people at large, precautionary principle is to be mandatorily adopted wherein the larger public interest must always give way to narrow corporate interests.

20. *It is to be noted that data regarding safety and efficacy of* the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) *has not been provided by the registration holders as under the law i.e.* Rule 30 (12) of the Rules, 1976, *the burden of proof is upon the person seeking to continue registration to advance data regarding the safety and efficacy of the drugs. It has been argued that the said drug has been freely available in the domestic market for years without any adverse effect being reported, which is proof enough of its safety and efficacy. However, the applicant could not share any adverse drug reporting system (pharmacovigilance system) in their company and the absence of such data might be the result of lack of reporting rather than serve as an evidence regarding the drug's safety and efficacy. Even otherwise, the absence of any adverse effects at one point of time is not a guarantee that it will not arise in the future and the statutory task of the regulator is to pre-emptively deter such a situation from ever occurring by applying the pre-cautionary principle.*

21. *It is also to be noted that pharmacovigilance data or even stability studies data is not the substitute of positive data regarding the safety and efficacy of drugs which has been universally accepted to arise only from valid clinical trials to be performed in accordance with the Bio-Study Rules, 2017.* In light of the above discussed, allowing the registration of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) to continue shall not be in the public interest as statutory intent of enacting the drug laws is the provision of safe and efficacious drugs and medicines to the people at large without any compromise. The task of the regulator is to curb any potential future menace from adversely affecting the public at large rather than responding belatedly to public health crisis which could have been mitigated by applying the pre-cautionary principle.

22. Director DTL Karachi dissented with the decision taken by the Board and opined not to suspend registration of these products.

Decision:

In light of the foregoing discussions, risk-benefit analysis and public health impact of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg), the Board made following decisions:

i. Suspended all drug registrations of the combination (Paracetamol 500mg, Thioridazine 3mg and Caffeine 70mg) under Section 7 (11) (b, c & d) read with Section 42 of the Drugs Act, 1976 in the larger public interest, with immediate effect as neither approved by any Reference Regulatory Authorities nor safety and efficacy data is available with any registration holder. Period of suspension will be for 1 year or till sharing of safety and efficacy data either by conducting clinical trials (to establish safety and efficacy) in accordance with the Bio-Study Rules, 2017 or approval by Reference Regulatory Authorities whichever is earlier. After provision of aforementioned data, cases of such pharmaceutical firms shall be considered on merit by the Registration Board.

ii. Suspended manufacturing and import of these drug products immediately and directed to withdraw available stocks from the market. QA&LT Division, DRAP will monitor and implement the decision in coordination with the respective provincial governments.

iii. Recommended Licensing Division, DRAP for approval of Qualified person for Pharmacovigilance (QPPV) / Local Safety Officer (LSO) whichever is applicable in licensed pharmaceutical units and advised PE&R and BE&R Divisions for similar action for importers of finished drug products as required under Pharmacovigilance Rules, 2022.

Case No.4. Review of Apremilast Tablet Range

Registration Board in its different meetings considered applications submitted for registration of different strengths of Apremilast Tablets. Detail is as under:

S/N	Status of Apremilast Tablets Considered by the RB				
	Meeting Reference	**Name of Applicant**	**Strengths Considered**	**Approval Status**	**Registration Status**
1.	M-272	M/s Crystolite Pharma, Islamabad	Apremist Tablet 30mg	Approved	Registration issued dated 22-12-2021 (R#111052)
2.	M-293	M/s S. J & G Fazul Ellahi (Pvt.) Ltd. Karachi	Ezla Tablet 10mg, 20mg & 30mg	Rejected	N/A
3.	M-296	M/s Navegal Laboratories, Hattar	Aprem Tablet 10mg & 30mg	Deferred for Submission of application on Form-5D along-with differential fee & submission of stability study data as per guidelines provided in 293rd meeting of Registration Board.	N/A
4.	M-307	M/s Tabros Pharma, Karachi	Pixel Tablet 10mg, 20mg & 30mg	Approved	Not yet issued.

In this regard, MRP of Apremilast 30mg tablet has been fixed **@Rs.3,559/4x14's** vide S.R.O. 1582(I)/2021 dated 09-12-2021.

Following information regarding "Apremilast Tablet" has been extracted from SmPC/ product monographs available on official web-sites of various RRAs:

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor i.e. indicated as a selective immunosuppressant for the treatment of Psoriatic Arthritis, Psoriasis and oral ulcers associated with Behçet's disease.

It has been approved by various reference regulatory authorities (RRAs) including USFDA, UK MHRA and TGA Australia in strengths of 10mg, 20mg and 30mg.

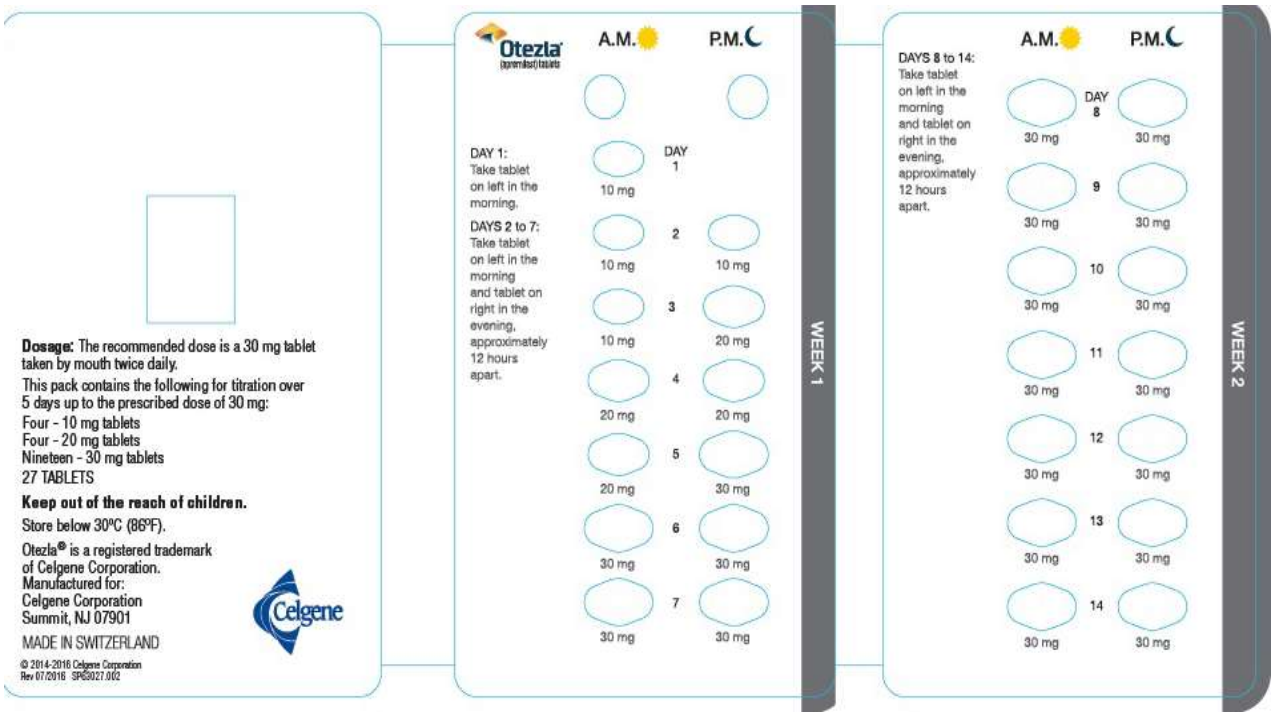
However, as per information available in RRAs, the recommended dosage and method of administration state that the treatment with Apremilast should be initiated by specialists experienced in the diagnosis and treatment of psoriasis, psoriatic arthritis or Behçet's disease.

Furthermore, the recommended dose of Apremilast is 30 mg taken orally twice daily, approximately 12 hours apart (morning and evening), with no food restrictions. In order to reduce the risk of GI symptoms, an initial titration schedule is required as shown below. No re-titration is required after initial titration.

Dose Titration Schedule										
Day 1	**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 6 & thereafter**	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10mg	10mg	10mg	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

Accordingly, USFDA states that the product will be packaged as bottles containing 60 tablets of 30mg strength for regular use and as a blister pack containing 10mg, 20mg and 30mg strengths as a 2-week starter pack for proper titration. Similarly, initial starter packs/ titration blister packs

have been approved by different RRAs. One of such example from USFDA has been placed as under:



Keeping in view the dosing/ titration schedule recommended by RRAs, instant case has been placed before the Registration Board for review of all previously granted approvals of Apremilast tablets.

Decision: **Keeping in view the reference product approved by RRAs which is available as "a blister pack containing Apremilast 10mg (4 Tablet), Apremilast 20mg (4 Tablets) and Apremilast 30mg (19 Tablets) as a 2-week starter pack for proper titration and a bottle containing 60 tablets of Apremilast 30mg for regular use", Registration Board made following decisions:**

i. **Show Cause notice shall be issued to M/s Crystolite Pharmaceuticals, Plot No. 1 & 2, Street No. S-2 RCCI Industrial Estate, Rawat Islamabad under section 7(11)(d) of the Drugs Act, 1976 that why the registration of their product Apremist (Apremilast) Tablet 30mg (Reg.No.111052) may not be cancelled. The management of the firm shall also be given the opportunity of personal hearing in the forthcoming meeting of the Board under section 42 of the Drugs Act, 1976."**

ii. **M/s Tabros Pharma (Pvt) Ltd. Plot No. L-20/B, Karachi Industrial Area, Sector-22, Federal B Area, Karachi shall be directed to revise/ standardize their applications of "Pixel Tablet 10mg, 20mg & 30mg" in line with the reference product approved by RRAs for further consideration of Registration Board.**

iii. **A reference shall be forwarded to DRAP's Authority regarding out of que consideration of fresh applications received in context with point (i) and (ii) above.**

= = = = = End of Document = = = = =