



## MONITORING DRUG-STORAGE TEMPERATURES AT LOCAL PHARMACIES

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**ABSTRACT** During the hot summer days of 2018, researchers at Apollo Institute of Medical Science & Research (AIMSR) in Hyderabad, conducted a randomised study, *for the very first time*, to monitor the drug storage room-temperatures, at 108 pharmacies, throughout the city of Hyderabad, South India. Expectedly, the mean room-temperatures at the pharmacies were recorded to be  $36.25^{\circ}\text{C}/97.25^{\circ}\text{F}$ : With a P value of  $<0.05$ , exposing drugs to temps way over the accepted standard of  $30^{\circ}\text{C}/86^{\circ}\text{F}$ . Exposure to excessive heat, other studies have shown, could damage drugs and diminish their potency. To safeguard, the authors suggest that drug-store owners take reasonable measures such as ventilate rooms and install air-coolers. To ensure compliance, the authors also suggest that the regulatory authorities (Drug Controllers) should spot-check room-temperatures and post excursions on DCA's Website, incentivise stores to install AC units, and conduct investigations to verify the fate and degradation of medicines when exposed to extreme heat—whether in storage or transport. Concluding, the authors reiterate that if compliance with guidelines can be improved; the current attitude towards temperature monitoring be contravened and public safety promoted, by heeding our recommendations, then, it would be remiss of us not to incorporate them. "After all, we are not discussing any ordinary subject; but, how we ought to safeguard the stability of precious medicines and the well-being of those who depend on them."

**KEYWORDS** : Drug-Storage; Temperature-Monitoring; Pharmacies; Hyderabad; India.

### INTRODUCTION:

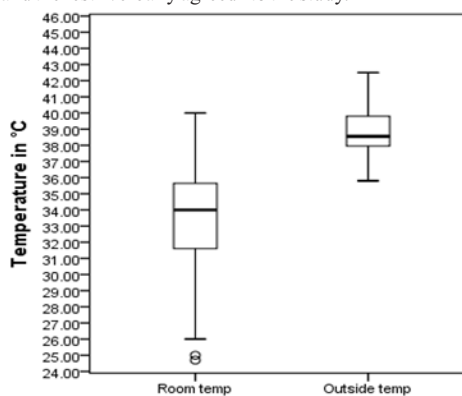
After obtaining approval of the Institutional Review Board (IRB), affiliated with Apollo Institute of Medical Sciences & Research (AIMSR) in Hyderabad in January 2018, we set out to ascertain the compliance, of drug-storage temperatures at randomly selected pharmacies, with compendial and labelling requirements: *Store at room temperature @  $15^{\circ}\text{--}25^{\circ}\text{C}$  ( $59^{\circ}\text{--}77^{\circ}\text{F}$ )*. Our reasons are two-fold: (1) Most regulatory bodies, national and international, require that medicines be stored at room temperatures unless specified otherwise in drug compendia or product labels. (2) There is insufficient data on the rates of compliance, at local pharmacies, with the regulatory requirements. Stated differently, while there is an abundance of data on *what should be done* to achieve optimal storage temperatures, the data are scant on *what is being done*, at pharmacy-stores in the conurbation of Hyderabad. To investigate the latter was, then, the purpose of this study.

### METHODOLOGY:

We used a random cluster sampling method to select 108 pharmacies (of 113 pharmacies, 5 refused to participate in the study) from the five wards or boroughs spread across the metropolis of Hyderabad. Designated pharmacy student *volunteers* from AIMSR were assigned to the specific task of measuring and documenting both the *outside temperature* across selected pharmacy stores and *inside temperature* where drugs are normally kept. The temperatures were measured by HTC "Easy Log" Temperature and Humidity Data Logger procured specifically for this study. All pharmacy visits were made, deliberately, during the hottest month of May between the hours of 11:00 am–4:00 pm IST (Indian Standard Time). The students were provided with uniform instructions on the use of the measuring devices and on the need to take permission from store owners or managers *before* speaking with the pharmacy staff or noting down room temperatures. Accordingly, the student volunteers documented their findings and relevant interactions on a study-specific template and submitted it to the assigned staff at AIMSR for record keeping. The survey commenced on 10May2018 and was completed on 24May2018. Afterward, a full statistical analysis, using **Independent Sample t-test and Whisker / Box Plots**, IBM SPSS-24, was completed by our resident statistician. To be sure, all data points were cross-checked by Dr. Prapthi Persis, one of the authors of this study.

### RESULTS:

Against the upper-limit of the *formal standard* for drug-storage ( $25^{\circ}\text{C}/77^{\circ}\text{F}$ ), **1.85%** (2 out of 108) of the pharmacies were compliant ( $P < 0.01$ ). Against the upper-limit of the *climatic conditions standard* ( $30^{\circ}\text{C}/86^{\circ}\text{F}$ ), **14.80%** (16 out of 108) of the pharmacies were compliant ( $P < 0.05$ ). The mean of room temperatures and road temperatures was computed to be  $36.25^{\circ}\text{C}/97.25^{\circ}\text{F}$ ;  $38.64^{\circ}\text{C}/101.5^{\circ}\text{F}$ , respectively (see figure 1). 54% of the pharmacies had air-conditioning (AC) units in their stores, 5% had air-coolers, and 41% had neither. 95% of the pharmacies had refrigerators. Expectedly, there was a statistically significant association between room temperature and AC. That is, rooms with AC units turned on were cooler than rooms without AC (see figure 2). The store-owners or managers of all 108 pharmacies gave permission for this study: 72 signed the consent form provided to them, and the rest "verbally agreed" to the study.



**Figure-1**

**Figure 1, Box-plot tracks the differences between room temperature (inside pharmacies) and road temperature (outside pharmacies). The median outside temperature was  $38.55^{\circ}\text{C}$  (lower & upper quartiles ranged from  $37.9$  to  $39.9^{\circ}\text{C}$ ). The median inside temperature was  $34^{\circ}\text{C}$  (lower & upper quartiles ranged from  $31.55$  to  $35.7^{\circ}\text{C}$ ).**

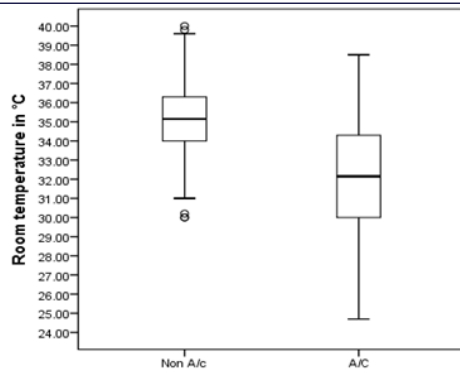


Figure-2

**Figure 2, Box-plot tracks the room temperature differences between pharmacies with Non-AC and AC. The median temperature of Non-AC rooms was 35.5°C (upper and lower quartiles ranged from 34 to 36.3 °C). The median temperature of AC rooms was 32.15°C (upper and lower quartiles ranged from 29.95 to 34.35 °C).**

### DISCUSSION:

Our study focused *only* on measuring the room temperatures at randomly selected (108) pharmacy stores where over the counter (OTC) and prescription drugs are normally kept, but not the freezer or refrigerator temperatures. We felt that our welcome would wear out quickly if we started rummaging through the refrigerators. Additionally, we had to reckon with two general standards: (1) Compendial and labelling standard, which is explicitly acknowledged; (2) Climatic condition standard, which is implicitly noted in the guidelines issued by the Government of India, Directorate General of Health Services and World Health Organization. In view of Hyderabad's extreme temperature conditions, we elected to analyse the results by the second: Climatic condition standard. By that standard, **81.64%** of surveyed pharmacies in the conurbation of Hyderabad were noncompliant with the temperature guidelines. Manifestly, the results violate all explicit and implicit guidelines on temperature control besides the grand principle of biomedical ethics: *Primum non nocere*. Another expected, yet statistically significant ( $P=0.008$ ), feature was noticed in our survey: Stores with functioning AC units fared better, at temperature controls than those without them. If confirmed by other equally well-conceived studies, we see a potential for a mandatory requirement to install AC units, at all pharmacies.

While we may sympathise with the pharmacy-store owners who routinely cope with power-cuts, effects of global warming and road-side pollution; we may not, perhaps should not, condone those who knowingly subject their precious cargo (be it medicines or milk) to the perils of extreme heat. Apropos to our discussion is the enquiry: *When we do not tolerate giving tainted milk (knowingly) to our babies for any reason at any time, why should we tolerate dispensing tainted medicines (knowingly) to those who have come to depend on them*—be it in Hyderabad or elsewhere in the world? The WHO guidelines on Storage of Essential Medicines singled out the following to be “unstable” under tropical (*Hyderabadi*) heat: acetylsalicylic acid; amoxicillin; ampicillin; penicillin V; paracetamol; ergometrine; methylergometrine; adrenaline; reconstituted antibiotics; retinol; nitroglycerine; levothyroxine; and others. The guidelines also point at the adverse effects of instability: Loss of assay and/or efficacy; change in dissolution pattern of solid dosage; separation of layers of liquid products; discolouration and *eventual degradation*.

These adverse effects are well known to pharmacologists and scientists involved in the storage and transportation of medicines. Hence, we opted not to conclude our study by rubbing in the untoward effects. We also refrained from reciting ceremonial shibboleths or blaming others for all that is going wrong in Hyderabad. As our esteemed readers would agree, they have all been tried before; but, to little avail. Instead, we elected to offer a few proactive measures, which have been proven successful in the Western democratic nations. Luckily, one need not have to travel out to the west to figure out their secrets. Indian pharmacologists, healthcare professionals, and scientists who worked in the advanced Western democratic nations or have familiarity with WHO's temperature and storage guidelines on investigational drugs and their comparators (prescription drugs, over the counter

medicines), would readily testify to a culture of zero-tolerance for temperature excursions. We are persuaded that we too can appropriate that spirit of zero tolerance, by instituting impartial and enforceable regulations. By that we mean common restraints which, when conjoined with our knowledge of its binding principles and laws, would lead us to make apposite decisions were we to apply them uniformly.

### RECOMMENDATIONS & CONCLUSION:

Judging by national and international guidelines, the results of our study confirm that over the counter (OTC) and prescription drugs, at **81.64%** pharmacies in and around Hyderabad, are exposed to higher than recommended temperatures. Such exposure, the guidelines warn, could render some drugs unstable and harm those patients who take them. We believe that the pharmacy stores which knowingly or perhaps lackadaisically dispense the unstable drugs; and the drug controllers, who knowingly or perhaps lackadaisically turn a blind eye to the goings-on, are complicit in the transgression of current regulatory and moral guidelines. When the pharmacy students of AIMSRS could monitor room-temperatures of pharmacy stores unobtrusively (with permission, of course) within minutes, we argue that the store owners can very well 'self-monitor' their own stores regularly if not randomly. As to the drug controllers, we recommend that they include in their monthly *to-do-list*: (a) monitor pharmacy-room and cold-storage temperatures; (b) incentivise stores to install AC units; and (c), coordinate further investigations to verify the fate and degradation of medicines when exposed to extreme heat. In addition, we suggest that DCA post its findings online for *we the people*, whom they serve, to see. Since citizens are the principal and permanent controllers of a democratic society, it is incumbent on those appointed to public offices to accommodate the needs of the electorate and be accountable to it. We could have expanded our survey and collected a true random sample of all the pharmacies within the twin-cities of Hyderabad and Secunderabad, thus fine-tuned our results even to a greater degree, had the DCA been open to sharing, *with the public*, the master-list of all pharmacies, pharmacy licensing requirements, and DCA's policy on drug transportation.

Despite the limitations, we nevertheless accomplished what we set out to do: To measure the differences between road-temperature outside pharmacy-stores and room-temperature inside pharmacy-stores, at selected pharmacies, with statistical precision. By design, we did not verify temperatures of the refrigerators stored inside the pharmacies, or the pharmacists' qualifications, or the fate of drugs when exposed to extreme heat. Of course, we expect the DCA or biopharma industry to pick up where we left off: Validate our findings and others mentioned above with, at least, two nation-wide randomised studies. If the results bear out, then issue standard operating procedures (SOPs) requiring all pharmacies, and all drug-transport vehicles, to install AC units with power back-up accoutrements. We should like to believe that other industries whose volatile cargo is also susceptible to extreme temperature excursions, such as high-end alcoholic beverages or perfumes, will take their cue from our study and others like it—and require temperature controls at all their storage facilities and on all their transportation vehicles.

Lastly, we are confident that—with the cooperation of individual pharmacy owners, the DCA, mass media, and the public at large—we too can promote a culture of *zero-tolerance*, thus step up to the international standards on drug-storage requirements. On that confidence, we wish to enquire: If the limitations in the prevailing temperature monitoring practices can be contravened; compliance with guidelines can be improved; public safety promoted by heeding our recommendations, then, would it not be prudent of us to step up and do the right thing, lest we may be held guilty of inaction? After all, the enquiry is not about any ordinary matter; but, how we ought to safeguard the stability of stored-medicines and the well-being of those who have come to depend on them.

### ACKNOWLEDGEMENT:

It's with a deep sense of sorrow we announce the sudden death of our resident statistician, Sivaiah Renangi, in the year 2019. Mr Renangi was an integral and important member of our team at AIMSRS, in Hyderabad. We acknowledge with gratitude his invaluable contribution to our paper. May his soul rest in peace.

### REFERENCES

1. Documentation on file at Apollo Institute of Medical Sciences & Research, Jubilee Hills, Hyderabad. Since both PI & CI are IRB members, they recused themselves during IRB

- deliberations of their proposal.
2. (a) Central Drugs Standard Control Organization. Guidelines on good distribution practices for pharmaceutical products, Ministry of Health and Family Welfare, Government of India, 2013, Directorate General of Health Services. (b) World Health Organization. Guide to good storage practices for pharmaceuticals, WHO Technical Report Series, No. 908, 2003, Annex 9. (c) Guidelines for Temperature control of drug products during storage and transportation (Guide 0069), Health Canada, 2005. (d) Code of Federal Regulations; Title 21, Volume 4; [Revised as of 01Apr2017] CITE: 21CFR203.32 – USA, and others.
  3. There is an abundance of data on the benefits of compliance with labelling requirements on storage, transportation temperatures of Investigational Products (IP), and on the burdens of non-compliance (Loss of assay; increase of impurity; separation of layers of liquid products; change in dissolution pattern of solid dosage; discolouration and eventual degradation of products). However, data are sparse on the prevailing temperature conditions at the local pharmacies besides occasional referential statements: "If you feel hot, your products are probably hot, too." There appears to be a greater emphasis on what should be the case rather than what is the case at local pharmacies. [Porter, William R., 2013. Degradation of pharmaceutical solids accelerated by changes in both relative humidity and temperature and combined storage temperature and storage relative humidity ( $T_{RH}$ ) design space for solid products. *J. Valid. Technol.* 19 (2).] Other references on file.
  4. From the East zone: Saroor Nagar circle and Gaddiannaram ward, were selected. From the South zone: Santosh Nagar circle and Santosh Nagar ward were selected. From the Central zone: Khairtabad circle and Somajiguda ward were selected. From the West zone: Chanda Nagar circle and Chanda Nagar ward were selected. From the North zone: Secunderabad circle and Tamaka ward were selected. We resorted to the cluster random sampling method after failing to obtain a 'master-list' of all pharmacies in Hyderabad from the office of Drugs Control Administration (DCA). We were informed by the regional drug controllers that the master-list of pharmacies is customarily not shared with anybody outside DCA.
  5. According to the manufacturer, the machines are calibrated to measure with 99% accuracy.
  6. The student volunteers (Mr. Pabba Deepak & Mr. Duggaraju Vydehi) were paid a reasonable allowance to cover incidental expenses per AIMSR's policy. The authors gratefully acknowledge the invaluable help extended by the volunteers.
  7. Ms. Swathi Sree, Executive Assistant to the Dean of AIMSR, received and collated students' responses.
  8. We are particularly grateful to Mr. Sivaiah Renangi (M.Sc., Statistics) at AIMSR, Hyderabad—for his advice on the merits of the systematic sampling method and his expert analysis of the study results.
  9. Op., cit. #2
  10. Since  $P < 0.01$ , therefore we conclude that there is a highly significant statistical difference of room mean temperature ( $32.24^{\circ}\text{C}$ ) from label temperature at  $25^{\circ}\text{C}$  used by t-test for one sample mean (sample size=108) at 1% Level of Significance.
  11. It appears that a latitude of  $5^{\circ}\text{C}/41^{\circ}\text{F}$  was allowed, for "climatic conditions," per Guidelines for Storage of Essential Medicines, both by national and international organisations. Op., cit. #2.
  12. Since  $P < 0.05$ , therefore we conclude that there is a significant statistical difference of room mean temperature ( $32.24^{\circ}\text{C}$ ) from label temperature at  $30^{\circ}\text{C}$  used by t-test for one sample mean (sample size=108) at 5% Level of Significance.
  13. Data on file in the Dean's office at Apollo Institute of Medical Science & Research Jubilee Hills, HYD.
  14. John Snow, Inc./DELIVER in collaboration with the World Health Organization. Guidelines for the Storage of Essential Medicines and Other Health Commodities. 2003. Page 63-64.
  15. Op., cit. #2
  16. Op., cit. #2 AND Quick JS, Rankin JR, Laing RO, O'Connor RW, Hogerzeil HV, Dukes MN, Garnett A, (editors). 1997. Managing Drug Supply. 2nd ed. West Hartford CT: Kumarian Press.
  17. Reddy, D.B. "Another Look at Respecting Patients' Autonomous Choices – In India." *Journal of Research in Medical Education & Ethics*, Vol. 6, No. 3, (November) 2016, pp-109-114
  18. Reddy, D.B. "Sustaining the Growth of Bioethics, In India." *Journal of Research in Medical Education & Ethics*, Volume-8, Issue-2 (July) 2018, p. 79-82.