



MONOCYTE ACTIVATION TEST (MAT): IDENTIFICATION OF MONOGRAPHS THAT RECOMMEND RABBIT PYROGEN TEST (RPT) AND BACTERIAL ENDOTOXIN TEST (BET) AS A KICK-OFF FOR SHOWING APPLICABILITY OF MAT

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Introduction

Injectable products must be pyrogen free since this kind of contamination may cause fever, shock or even death¹. The first important toxicological assay developed for the detection of pyrogen contamination of injectable products was the Rabbit Pyrogen Test (RPT). Bacterial Endotoxin Test (BET), also known as *Limulus* Amoebocyte Lysate (LAL) was taken as a replacement for RPT, but, it detects only endotoxins and some interferences may occur on the reaction depending on the products tested, specially biologicals^{1,2}. Monocyte Activation Test (MAT) was introduced in the European Pharmacopoeia in 2010 as a third assay for detecting pyrogenic contamination.

MAT is thought to be a good replacement for RPT, however ICCVAM stated that: I – MAT was not adequately evaluated to detect endotoxin in a sufficient number and range of parenteral pharmaceuticals and in no biological products and medical devices; II – there is no sufficient data that support the ability to detect non-endotoxin pyrogens; and III – it can be considered to detect pyrogen in human parenteral drugs on a case-by-case basis, subject to validation for each specific product³.

Objective

Identify which products are requested for Rabbit Pyrogen Test and/or Bacterial Endotoxin Test to serve as a schedule for testing Monocyte Activation Test applicability.

Method

Each Monograph in the United States (USP), European (Eur. Ph.) and Brazilian (Braz. Ph.) Pharmacopoeias were evaluated and checked about requiring RPT and/or BET. Products were listed in an MS-Excel® plan.

Results

RPT is required for 20 Monographs in USP, 37 in Eur. Ph. and 32 in Braz. Ph. (Figure 1) and BET appears in 619 Monographs in USP, 157 in Eur.Ph and 48 in Braz.Ph. (Figure 2), including drugs, biologicals and medical devices. Three products require pyrogenicity in the 3 Pharmacopoeias. Both RPT and BET are recommended by 6 Monographs in Braz. Ph. and 15 in Eur. Ph. and it is allowed to choose which test is to be applied. In Braz. Ph, most are biologicals (vaccines and hyperimmune sera), so, these products should be the first ones to be tested for the applicability to MAT since they are tested mainly by RPT.

References

- ¹ MELANDRI, V; FARIA, G; CALDEIRA, C; PRESGRAVE, O. Utilização de métodos alternativos na determinação da contaminação pirogênica no controle de produtos injetáveis sujeitos à Vigilância Sanitária. **Universitas: Ciências da Saúde**, Brasília, v.8, n.2, p. 69-95, jul./dez, 2010
- ² SCHINDLER S, VON AULOCK S, DANESHIAN M, HARTUNG T. Development, validation and applications of the Monocyte Activation Test for pyrogens based on human whole blood. **ALTEX**; 26: 265-77, 2009.
- ³ ICCVAM. Intergency Coordinating Committee on the Validation of Alternative Methods. Validation status of five *in vitro* test methods proposed for assessing potential pyrogenicity of pharmaceuticals and other products.. **ICCVAM test method evaluation report**, NIH publicatio, n. 08, p.6392, 2008.

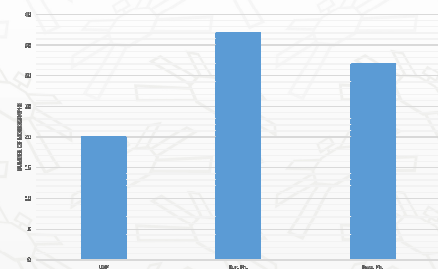


Figure 1 – Number of monographs in the United States Pharmacopoeia (USP), European Pharmacopoeia (Eur. Ph.) and Brazilian Pharmacopoeia (Braz. Ph.) that require Rabbit Pyrogen Test (RPT).

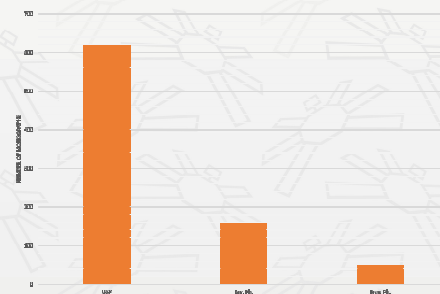


Figure 2 – Number of monographs in the United States Pharmacopoeia (USP), European Pharmacopoeia (Eur. Ph.) and Brazilian Pharmacopoeia (Braz. Ph.) that require Bacterial Endotoxin Test (BET).

Conclusion

Taking into account these ICCVAM statements, a collection of data referring to Pharmacopoeial Monographs that indicate a need for pyrogenicity analysis may be used as a kick-off for a study of the applicability of MAT to other products such as biologicals, as well as for studying the response of MAT to other non-endotoxin pyrogens.

In Braz.Ph, most of the monographs that require RPT are those referred to biologicals, so, these products should be the first ones to be tested for the applicability to MAT since they are tested mainly by RPT.