ON PARENTERAL FORMULATIONS AND GOLDEN STANDARDS FOR QUALITY AND SAFETY

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Injectable products inevitably contain very small amounts of subvisible particulate matter (i.e., synthetic polymers, starch, metal ions, insoluble degradation products, etc.); guidelines to the assessment and control of such contaminants are reported in U. S. Pharmacopoeia (USP) and in European Pharmacopoeia (EP). In fact, an excessive quantity of particulate matter could cause adverse drug reactions (ADRs). The ADRs induced by injectable formulations may be more frequent and severe in critical patients and are difficult to be recognized and thus represent a severe matter from both ethic and economic viewpoints. Clinical evidence indicates that intravenous (iv) treatments with lower levels of particulate contamination are associated with a reduction in the incidence of ADRs. Piperacillin/tazobactam is a combination of antibacterial drugs indicated for nosocomial pneumonia caused by piperacillin-resistant, ß-lactamase producing strains of *Staphylococcus aureus* and by piperacillin/tazobactam susceptible *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. An injectable formulation contained piperacillin/tazobactam has been patented and is marketed by Wyeth (ZOSYN® in USA and TAZOCIN® in almost all Europe), and represents one of more effective therapeutic option for treatment of nosocomial infections (consumption data: 9.7%, 12.2% and 14.76% of the total injectable antibacterial drugs in 2004, 2005 and 2006, respectively). To further ensure the due quality standard for injectable formulations introduced by USP and EP, in 2005 this formulation was modified by the Company through addition of citrate buffer and EDTA as excipients, to improve formulation robustness against pH drop on storage (leading to precipitation of insoluble piperacillin acid) and degradation of the dissolved drugs in presence of metal ions (particularly zinc that enhances the beta-lactam ring opening of piperacillin and forms insoluble complexes with piperacillin). Until today no ADR for excessive quantity of particulate matter in this formulation has been reported. During 2007, the piperacillin/tazobactam patent will expire and the generic piperacillin/tazobactam formulation may be marketed. In Italy, generic drugs allow a considerable saving of economic resources. Of course also the generic piperacillin/tazobactam formulation can allow the SSN to save considerable resources, to be differently allocated in the complex management of public health; but to avoid risks for patient health and also additional consumption of economic resources (needed to treat possible ADRs), it has to warrant the same high standard of quality and safety as well as the brand-name drug.