Brief overview of use of oil-in-water emulsions as adjuvants for influenza vaccines

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The most advanced o/w emulsion adjuvants

- Emulsions of oil-in-water.
  - AS03 (GSK)
    - squalene 10.68 mg, DL-α-tocopherol 11.86 mg, polysorbate 80 4.85 mg [(1)]
  - MF59 (Novartis)
    - squalene 9.75 mg, polysorbate 80 1.175 mg, sorbitan trioleate 1.175mg [(2)]
  - AF03 (Sanofi Pasteur)
    - Squalene-containing emulsion (2.5% emulsion)
  - Other companies also developing squalene-based adjuvants
  - Each emulsion is different therefore safety and efficacy to be viewed separately !

1) From Prepandrix dossier
2) From Focetrea dossier

Mechanism of action

- Exact mechanisms not yet fully elucidated.
- MF59: Two proposed mechanisms [1]
  - Antigen delivery
  - Indirect immune potentiation (via JunB and Ptx3) and APC recruitment and activation.
- AS03: no publicly available data.
- AF03: no publicly available data.
  - preclinical studies show reversible inflammatory changes including increase in white blood cells

1) Mosca et al. *Proc. Natl. Acad. Sci USA*, 2008

Clinical use: MF59 in influenza vaccines

- Fluad™
  - seasonal influenza vaccine with MF59 for older adults. Marketed in 26 countries. >40M doses distributed
    - No publicly reported safety signals
- Clinical trials with influenza vaccines:
  - 13000 elderly, 6000 adults, 700 children (6 Mo-17yr)
    - Marginal but significant increase in local and systemic reactogenicity
    - No increase in % of subjects reporting AEs (compared to non-adjuvanted influenza vaccine) including autoimmune disease, cardiovascular diseases, serious adverse events, hospitalizations, and death.

Clinical use: AS03 in influenza vaccines

- >45000 individuals vaccinated with AS03-containing vaccines.
- Safety data in approximately 15400 analyzed subjects with ≥ 6 months follow-up, and over 22,000 additional subjects in ongoing trials
- integrated summary of safety (5 blinded/controlled and 3 open-label trials; ages 18-93 yrs)
  - Some increased short-term reactogenicity, esp. injection site pain
  - Predominantly mild and transient, no escalation with 2nd doses,
  - Evaluation of potential immune-mediated events limited by small numbers of events and unbalanced randomization of subjects. However, after review of existing data, no safety concerns were identified in this class
    - Potentially immune-mediated events occurred in H5N1/AS03 recipients at rates compatible with other clinical trials experience and also literature estimates of incidence/prevalence
    - No clear temporal pattern was observed with small numbers of cases
    - Pediatric data are currently limited, but qualitatively similar to adult data.

GSK AS03-Influenza Vaccine Safety Approaches

- GSK is using a standardized approach for pre-licensure trials:
  - Solicitation of local and systemic reactogenicity for 7 days after each dose (CBER, Brighton Collaboration grading scales)
  - Serum chemistry and hematologic monitoring in early trials
  - Unsolicited adverse events with special focus of medically-attended and serious AEs through 6 to 12 months after exposure
  - Pro-active evaluation of adverse events of special interest and potential immunologically-mediated events by:
    - Use of expanded “immune-mediated disease” eCRF tool to collect detailed case histories
    - Database queries built on 120 MedDRA PTs capturing classical influenza vaccine issues (e.g., GBS, facial palsy), and a broad spectrum of immunologically-mediated diseases.

Clinical use: AF03 in influenza vaccines

- 2 phase 1 clinical trials
  - 513 adults
  - Higher incidence of injection site reactions
  - No differences in systemic events

Theoretical concerns

- Anti-squalene antibodies (claimed association with 'gulf-war syndrome')
  - Addressed by GACVS (July 2006)
  - The Committee concurred that fears of squalene in vaccine-inducing pathological anti-squalene antibodies are unfounded. It did note, however, that the experience of squalene-containing vaccines has been primarily in older age-groups and recommended that as squalene-containing vaccines are introduced in other age-groups, careful post-marketing follow up to detect any vaccine-related adverse events needs to be performed.
    - WHO Weekly Epidemiological Record on 14 July 2006