Setting Default Health-Based Exposure Limits for Early-Stage Monoclonal Antibody-Based Therapeutic Proteins

Poster Board No. P621
Abstract No. 2239

HMS Adragna, JC Gould, K Sachdeva, and RG Sussman
SafeBridge Consultants, Inc., New York, NY

Abstract

Health-based exposure limits (HBELs) are developed for active pharmaceutical ingredients to minimize product cross-contamination in GMP manufacturing facilities (acceptable daily exposures, ADEs) and to identify acceptable exposures for worker protection (occupational exposure limits, OELs). In the absence of sufficient data to support a robust, compound-specific assessment and derivation (*e.g.*, early in the development of the drug candidate), default HBELs may be assigned. However, standardized methodologies for the establishment of default limits for biotechnology-derived products such as recombinant proteins and monoclonal antibodies (mAbs) have not been previously described. Robust data sets from 54 marketed mAb-based therapeutic agents were evaluated to derive ADE and OEL values utilizing the lowest therapeutic dose, bioavailability, and standard adjustment factors. Three Hazard Categories were identified, based on special considerations and an analysis of the HBEL values. Recommendations were developed for assigning default ADE and OEL values of 0.1, 1, 10, 100 µg/day or µg/m³ for early-stage mAb-based therapeutics, taking into account the assigned Hazard Category and potency. The criteria on mechanism of action, potency, and bioavailability should be reviewed by a qualified toxicologist, and the limitations of the assessment should be understood when assigning default values to ensure these are protective of the patient population and/or workers, as appropriate. Limitations, including predictability of hazards for novel therapeutic targets and unpredictable adverse effects, should be understood. As the Hazard Category and the human dose may change as more information becomes available, there should be vigilance to ensure the defaults are updated and/or replaced with more robust, compound-specific derivations when sufficient data are generated.

Background

Acceptable Daily Exposures (ADEs) and Occupational Exposure Limits (OELs) are two types of HBELs developed for active pharmaceutical ingredients. ADE values represent a dose unlikely to cause adverse health effects (including desired pharmacology) in patients exposed by cross-contamination to drug residue from a previous batch, and OEL values represent an airborne concentration protective of the health of workers who may be exposed up to 8 hours per day, 40 days a week, for their working lifetime [1-6]. The process of determining product-specific ADE and/or OEL values involves comprehensive review of available clinical, pharmacological, and toxicological data. A point-of-departure (POD) is identified, traditionally defined by the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL). In the absence of sufficient data to support a compound-specific assessment, default limits may be assigned [7]. However, standardized methodologies for the establishment of default limits for biotechnology-derived products such as recombinant proteins and antibodies have not been previously described.

Development of Default ADE and OEL Values

- Data for 54 marketed proteins were gathered from public literature [8], including therapeutic target, mechanism of action, dose, pharmacokinetics, and adverse effects.
- The proteins were assigned a hazard category based on the specified considerations (see *Hazard Categories*).
- Estimated ADE/OELs were calculated, using the lowest therapeutic dose adjusted to a daily dose, as the Point of Departure.
- Adjustment and modifying factors were based on hazard category, and general assumptions on proteins and pharmaceutical agents.
- Inhalation bioavailability (BA) was assumed to be 1% for the OEL [9].
- Trends in the data were used to identify conservative default values, based on hazard category and dose.

Typical Calculation for HBELs

$$\text{ADE} = \frac{\text{PoD [× BW]}}{AF_C \times \alpha \times S \times MF} \qquad \text{OEL} = \frac{\text{PoD [× BW]}}{AF_C \times \alpha \times S \times MF \times V}$$

Where:

- PoD = Point of Departure, *e.g.*, a therapeutic dose, or a no- or lowest-observed-adverse-effect level (NOAEL or LOAEL) for the critical effect [1,10-12]
- BW = body weight (50 kg for an average patient [2,3] or 70 kg for a worker [13])
- AF_C = a composite adjustment factor of $AF_H \times AF_A \times AF_S \times AF_L \times AF_D$
- α = adjusts for the bioavailability between different routes of exposure
- S = adjusts for accumulation potential
- MF = a modifying factor to account for residual uncertainties not covered by AF_C
- V = the volume of air inhaled during the assessed period (OEL only) 10 m^3/day for an 8-hour work shift for a 70-kg adult doing moderate work [13,14].

Adjustment factors used to determine AF_C include:

- AF_H = Intraspecies differences (variability among humans)
- AF_A = Interspecies differences (extrapolating from animals to humans)
- AF_S = Sub-chronic-to-chronic (adjustment for length of study)
- AF_L = LOAEL-to-NOAEL (if a NOAEL was not identified)
- AF_D = Database completeness

Adjustment Factors for Estimated ADEs/OELs

Adjustment factor	Default Value	Value Used	Comment	
Intraspecies differences (AF_H)	10	10	Default for the general population	
Interspecies differences (AF_A)	1 – 12	1	Human data	
Sub-chronic-to-chronic (AF_S)	3	1	Well studied Ab-based therapeutics with chronic exposure data available	
LOAEL-to-NOAEL (AF_L)	3	5	LOAEL – lowest therapeutic dose as POD	
Database completeness (AF_D)	3	1	Dataset generally considered adequate for assessment of Ab-based therapeutics	
Modifying Factor (MF)	1	1 5 10	Low Moderate Severe	Severity of effect
AF_C x MF		50 250 500	Low - Hazard Category 3 Moderate - Hazard Category 2 Severe – Hazard Category 1 / 1a	

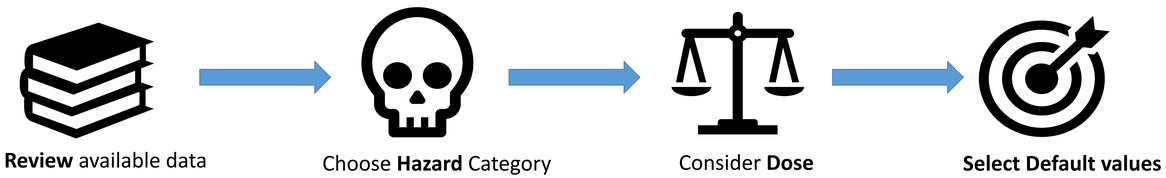
Estimated HBELs for Select Proteins*

Generic Name	Target	Activity Description	Hazard Category	Route	Lowest TD	AF	ADE POD mg/day	ADE µg/day	OEL POD mg/day	OEL α	OEL µg/m³
blinatumomab	CD3(B) - CD19(T)	Oncology, CRS/premedicate	1a	IV	0.009 mg/day	500	0.009	0.02	0.009	0.1	0.2
benralizumab	IgG1/k-class, IL-5Rα	IM stim, ADCC asthma	1	SC	30 mg/8wk	500	0.5	1	0.8	0.1	15
raxibacumab	anthrax	non-human premedicate	1	IV	40 mg/kg (single)	500	2000	4000	2800	0.1	56000
denosumab	RANKL	osteoporosis	2	SC	60 mg/6mo	250	0.33	1	0.46	0.1	18
belimumab	BLyS	IM suppress	2	IV	10 mg/kg/2wk	250	36	143	70	0.1	2800
alirocumab	PCSK9	CV - lipid	3	SC	75 mg/2wk	50	5	107	8	0.1	1500
idarucizumab	dabigatran	antidote	3	IV	5 g	50	5000	100000	5000	0.1	1000000

* The information on each compound was obtained from the FDA Label [8]. Full list of compounds and supporting information is available as a supplemental document.

** Abbreviations: CD – cluster of differentiation; (B) – B-cell; (T) – T-cell; Ig - immunoglobulin; IL-5Rα – interleukin-5 receptor alpha subunit; RANKL – receptor activator of nuclear factor kappa-B ligand; BLyS – B lymphocyte stimulator; PCSK9 – proprotein convertase subtilisin kexin type 9; CRS – cytokine release syndrome; IM – immune, stim – stimulatory; ADCC – - dependent cell-mediated cytotoxicity; CV – cardiovascular; IV – intravenous; SC – subcutaneous, TD – therapeutic dose; BA - bioavailability

Method to Set Default HBELs for Early Development Proteins



Hazard Categories

Hazard Category 1 – High Concern

- Immune-stimulatory activity (*e.g.*, PD1, CTLA-4) that may increase the potential for hypersensitivity response or result in impaired maintenance of pregnancy
- ADCC or CDC mechanism of action (*e.g.,* IgG1; CD20)
- Oncology indications
- Reproductive or developmental toxicity potential based on the mechanism of action (*e.g.*, vascular endothelial growth factor; VEGF)
- Immune-mediated hypersensitivity responses
- Premedication with anti-inflammatory agents.

Hazard Category 1a – Very High Concern

- Specific immune receptor targets with potential to induce cytokine release syndrome (CRS)
- Novel mechanisms of action not previously described

Hazard Category 2 – Moderate Concern

- Immune-inhibitory activity (*e.g.*, cytokine or immune cell receptor targets) that may lead to infection or formation of tumors after prolonged exposure
- Target present in the general population with a particularly concerning outcome (*e.g.*, increased blood coagulation)

Hazard Category 3 – Low Concern

- Exogenous targets (*e.g.,* fungus bacteria, virus)
- Less concerning target or pharmacological mechanism (*e.g.,* lipid metabolism).

Recommendations for Default Values

Default	Lowest Therapeutic Dose (mg/day)		
ADE µg/day	Hazard Category 1/1a	Hazard Category 2	Hazard Category 3
0.1	≤0.5	≤0.3	≤0.05
1.0	**≥0.5 D***	**≥0.3 D***	≥0.05
10	≥5	≥3	≥0.5
100	≥50	≥25	**≥5 D***
OEL µg/m³	Hazard Category 1/1a	Hazard Category 2	Hazard Category 3
0.1	≤0.05	≤0.03	≤0.005
1	≥0.05	≥0.03	≥0.005
10	**≥0.5 D***	**≥0.3 D***	≥0.05
100	≥5	≥3	**≥0.5 D***

* D – Use as default with no human dose information

Summary

- **HBELs are needed in pharmaceutical R&D for patient and worker protection.**
- **Standardized methodologies for setting HBELs for early-development protein-based therapeutics have not been previously described.**
- **54 marketed protein therapeutics were evaluated based on hazard and projected averaged daily dose to develop default HBELs.**
- **This method is designed to be conservative in nature in order to be protective when information is limited.**
- **A compound-specific HBEL should be determined when there is sufficient data to do so.**
- **This approach was not designed for peptides or proteins conjugated to other substances (*e.g.*, antibody drug conjugates, oligonucleotides, radionuclides, *etc*).**
- **As validated quantitative methods for air and surface sampling of large proteins are limited, this method is intended to guide containment procedures.**

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Conflict of Interest: Authors were employed by SafeBridge Consultants at the time this evaluation was conducted. The majority of this work was sponsored by an entity that manufactures and/or distributes materials that are the subject of this poster.